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RECENT DEVELOPMENTS OF KNOWLEDGE OF LIVER FUNCTION AND BEHAVIOUR.[1]

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THE liver is made up of a parenchyma, blood vessels and ducts. The parenchyma consists of a uniform lot of epithelial cells arranged in simple columns and grouped around blood vessels and ducts into what are commonly called lobules; only in occasional animals are these lobules found to be separated the one from the other by connective tissue. The blood supply of the organ is apparently dual; but a great deal of evidence[(1)] points to the conclusion that the hepatic artery breaks up into capillaries which supply the bile ducts and other structures in the portal canals, the blood being collected from these capillaries to drain into the portal vein, and to give the sole supply to the parenchyma from the portal vein. The amount of blood flow for the whole liver has been determined as about 30 cubic centimetres per kilogram per minute in laboratory animals; this is a slow rate and may account for the high temperature of the liver. It has been proved by McMichael[(2)] that in the rabbit the major supply of oxygen for the liver is from the hepatic artery; but in the high blood pressure animals such as the cat and dog, and presumably in man, the main supply of oxygen comes from the portal vein; but in conditions of shock the main oxygen supply comes from the hepatic artery.

Regeneration of Liver Tissue.

It has been proved that regeneration of liver tissue takes place readily in laboratory animals after a portion of the liver is removed.[(3)] In animals such as the rat and rabbit the rate of regeneration is astonishing, one-third of the liver growing to the original size of the liver in three weeks. In cats and dogs the rate is somewhat slower. A point of interest is that the presence of the pituitary gland and its hormones is not essential for this growth of the liver.[(4)] The question arises as to whether regeneration takes place in the case of humans. There are recorded instances in which this has been tested. One instance seen by the present author was in a man from whom a large hydatid cyst of the right lobe of the liver had been surgically removed twenty years before death, which resulted from extensive ulceration of the duodenum. The man was in an emaciated state, yet the left lobe of the liver weighed 35 ounces; this was the same weight as that of the liver (Figure I) of a patient suffering from pyloric obstruction who died at about the same time. It may be mentioned that in experimental inanition by starvation the liver may be reduced to 40% of its original weight.[(5)] This liver illustrated also the interesting point raised by Cantlie,[(6)] that the two branches of the portal vein supplied quite discrete portions of the liver (Figure II), the line dividing them being from the middle of the fossa of the inferior *vena cava* to the middle of the fossa of the gall-bladder. The whole of the liver to the right of this line was absent except for a few bile ducts on the wall of a small nodule of fibrous tissue enclosing hydatid remnants. The left lobe was approximately the size of a normal liver, and when the cells were counted, had the same number of cells per unit area as the liver in the case of pyloric obstruction that has been mentioned. It had the same number of portal canals per unit area also, so that one may draw the conclusion that not only was there an increased mass of liver growing from the left lobe (the ordinary weight of which would have been 16 ounces in a good state of nutrition), but that this regenerated liver had also normal-sized lobules and a normal cell density—that is, there had been an increase in the number of cells and they had been rearranged into normal-sized lobules.

[1] Read at a meeting of the Victorian Branch of the British Medical Association on October 15, 1941.

It would appear from this case that there is a parenchymatous barrier between the right and left halves of the liver, and that agents producing simple pressure in one-half of the liver are restricted by this barrier from encroachment into the other half of the liver (Figure III). It is of interest to know how such pressure within the liver substance gives rise to degeneration of the liver. It can be demonstrated quite readily[7] that ligation of the portal vein branch to one-half of the liver of animals such as the rat and rabbit will result in a complete atrophy of that half of the liver, only remnants of bile ducts in fibrous tissue being left. In the case of the cat and dog this atrophy is much slower than in the smaller animals, but is eventually almost complete. Ligation of the bile duct draining one-half of the liver also results in an atrophy of this part of the liver and in a growth of the functionally intact part of the liver similar to that resulting from ligation of the portal vein.[8] On injection of the vessels leading into a portion of the liver the bile ducts from which have been tied, we[9] have found that the hepatic artery can be injected

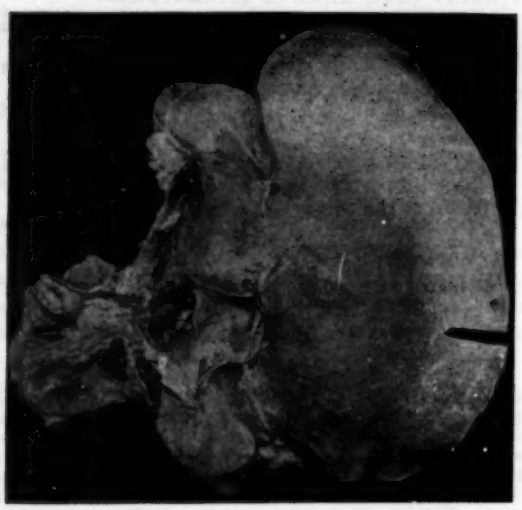

FIGURE I.

View of the inferior surface of the liver mentioned in the text. The left lobe, quadrate lobe and caudate lobe are shown. The remnants of the gall-bladder present on the right of this mass and the opening of the hepatic veins into the inferior *vena cava* show the extent to which the right lobe was destroyed. The remnants of the hydatid cyst are present in the left lower part of the picture.

quite satisfactorily with coloured gelatin, but that the portal vein is almost obliterated. It would appear likely that ligation of the bile duct in this case produces its result by setting up in the portal canals increased pressure which causes a constriction of the portal veins, and so the mechanism of production of atrophy is similar to that produced by ligation of the portal vein. One may conclude therefore that it is most likely that abnormal growths producing simple pressure within the liver produce atrophy by blocking off the portal blood supply in that portion of the liver in which the abnormal tissue is growing.

The next feature of importance in regeneration is that the part of the liver which normally would regenerate does not do so if its portal blood supply is diverted or if its bile ducts are ligated.[7] It is apparent, therefore, that portal venous blood is necessary for the normal regeneration of liver tissue, and it is found that regenerated liver tissue grows a new supply of blood vessels from the portal vein. In some cases of cirrhosis, the appearances would lead one to believe that one of the reasons why adequate regeneration of liver does not take place is either that the main venous channels are constricted by the fibrous tissue, or that the bile ducts are constricted by the fibrous tissue with resultant obstruction to these channels, and associated with the pressure developing in them there is a failure of growth of the portal blood supply to newly developing parts of the liver.

FIGURE II.

Liver injected with blue ink (photographed as white) via the right branch of the portal vein. The upper mass is a coronal section; the lower mass shows the inferior surface of the same liver. The discrete separation of the two parts of the liver by a line from the *venæ cavæ incisura* to the middle of the gall-bladder fossa is illustrated.

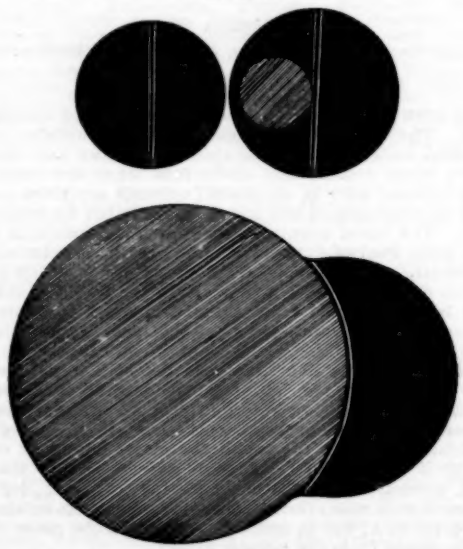

FIGURE III.

Diagrammatic representation of the parenchymatous barrier between two lobes of the liver; the over-growth of the unaffected lobe is illustrated.

In view of the fact that newly developed liver tissue is supplied by the portal vein, it is of interest to know whether all newly-grown tissue in the liver is supplied from

the same source. In a series of livers from autopsies it was demonstrated[21] that all newly developed tissue which had a fibrous tissue stroma developed in the liver a blood supply from the hepatic artery. It would appear, therefore, that the more rapid rate of growth of metastases in the liver than elsewhere, as demonstrated by Willis,[220] is probably due to the fact that the temperature in the liver is as much as 2° F. higher than in other organs.

From the evidence it appears perfectly safe to draw the conclusion that in the case of man liver tissue can regenerate until a normal amount of liver tissue is present. This has two important clinical applications: (i) Livers containing abnormal growing tissue become very large organs because the amount of liver tissue does not decrease, though it may become redisposed. (ii) One may, in the case of a slowly growing tissue such as a hydatid cyst, take it for granted that unless obstruction of the bile duct also is present, there will be a normal amount of liver tissue. This statement raises the question of refusing to perform an operation because the size of the hydatid cyst would suggest that there would be an inadequate amount of liver tissue to tide the person over the operation. These observations indicate that it would require an extremely rapidly growing destructive agent to produce such a condition.

The Liver in Metabolism.

The importance of the liver in the intermediary metabolism of substances in the body is becoming more and more evident with the greater refinement of techniques employed for investigation. It is well known that the liver forms glycogen from ingested glucose and gives up that glycogen to the blood stream. These observations of Bernard have never been questioned. The amount of glycogen which is present in the liver varies apparently during the day, and is to some extent related to the ingestion of carbohydrate. It is important, however, to realize that though the variations in the concentrations of glycogen in the liver are much greater than those in the muscle, when one allows for the much greater mass of the muscle it is evident that there is an equal storage of glycogen in the two sites. An equally important consideration is that the liver can form carbohydrates from amino-acids. We have, then, the following plan:[23,24,25,26] Ingested hexoses are stored in the liver and other tissues, especially the muscles, as glycogen. Insulin is necessary for the glycogen storage, and the amount of insulin secreted from the pancreas is apparently governed mainly by the level of the sugar in the blood circulating through the pancreatic blood vessels; but there is some neuro-effector mechanism affecting the amount of this secretion. Hormones from the adrenal cortex and the anterior lobe of the pituitary gland also affect this laying down of glycogen, but they will be considered later.

The next feature of importance is that the liver does not burn all the glycogen laid down in it; but when the sympathetic nerves to it are stimulated, or when adrenaline is secreted into the blood-stream, or perhaps when the glucose content of the blood flowing through its vessels is reduced, the liver secretes glucose into the blood-stream. This glucose is then taken up elsewhere by other tissues, especially by muscle. The muscles, however, do not give up glucose to the blood stream. A certain amount of lactic acid may escape from them during exercise; but this is probably taken up by other muscles, especially the heart, and synthesized to glycogen.

It is thus evident that the glycogen stored by the liver after a meal will soon be passed into the blood stream and used up by the tissues. The glycogen content of the liver does not, however, fall very low, even after twenty-four hours' fasting. This glycogen is not derived from ingested carbohydrate. All available evidence indicates that it is formed from amino-acids and perhaps from fatty acids by the liver, a process to which the term "gluconeogenesis" has been given. The control of this activity of the liver is apparently a complex one. In the absence or relative deficiency of insulin the liver produces great quantities of glucose from amino-acids, and as the storage of glucose is also defective in the absence of insulin the blood sugar level is high, and a large part of this sugar and all of the corresponding nitrogen are excreted in the urine. If, however, pancreatectomy is performed on an animal from which the adrenal or pituitary glands have been removed, the blood sugar level does not rise so high and the excretion of dextrose and nitrogen is also less. Administration of adrenal cortical hormones will restore the diabetic condition in the animal lacking adrenals and pancreas, and to a submaximal extent in the animal from which the pancreas and pituitary have been removed. Certain extracts of the pituitary will cause a recrudescence of the diabetes in the animal lacking pancreas and pituitary, but have only slight action in the animals from which the adrenals have also been removed. In these animals, however, the administration of cortical hormones and the appropriate pituitary extracts causes the diabetes to become as severe as in the animals from which the pancreas has been removed.

Evidence that the pituitary substances affect gluconeogenesis *per se*, and not only by an effect on the suprarenal cortex, which is atrophic in animals, from which the pituitary has been removed, is best seen in the case of the fasting glycogen content of the liver and muscles of animals from which the adrenals or the pancreas and adrenals only have been removed. In the animals which have normal electrolyte concentrations and from which the adrenals have been removed, the fasting glycogen content of the liver is extremely low, presumably owing to failure of replenishment through gluconeogenesis. Cortical hormones will restore the level of the liver glycogen and of the blood sugar. In the animals from which adrenals and pancreas have been removed, pituitary extract does not cause redevelopment of the severe diabetic state; but if this is brought about by cortical extract, pituitary extracts then aggravate the condition. The suprarenal cortex and the anterior pituitary gland appear to be balanced against insulin in the maintenance of blood sugar levels in the animal which has used its carbohydrate food substances. The final effect appears to depend on relative concentrations rather than on the absolute concentrations of the hormones present. This is well seen in the production of permanent atrophy of the pancreatic islet tissue of dogs to which repeated large doses of crude extract of anterior pituitary gland are given. The islets secrete excessive quantities of insulin for a short period, but then atrophy from "exhaustion". Such atrophy does not take place in the rat, apparently because the islet tissue increases so rapidly that "exhaustion" does not take place. A pituitary hormone (pancrootropin) has been suggested to explain this. Best's[28] observations that the atrophy can be avoided by the administration of large doses of insulin or by fasting or fat feeding the animal to which the pituitary extract is given, indicate the advisability of adequate insulin administration for the diet selected in an acute onset or an exacerbation of diabetes.

Rigid control of the electrolyte concentrations in these experiments is necessary, because it has been observed[29] that in diabetics deprivation of sodium in the diet leads to an increased requirement of insulin, and that if the diet is amended to include an adequate amount of sodium the carbohydrate metabolism can be stabilized with a reduced amount of insulin. The level of potassium in the diet also affects the carbohydrate metabolism, but in the opposite direction to that of sodium. Whether or not the failure of gluconeogenesis is related to the fatigability of muscles in adrenalectomy is not yet decided. The liver also plays a part in the removal of lactic acid from the blood stream. Experiments that have been performed on animals lead one to believe that the liver plays a very small part in this mechanism, except when the animal is in a fasting condition, when the liver apparently does take up considerable quantities of lactate from the blood.[27] The other point of interest here is the formation by the liver of ketone bodies. It has been demonstrated[30] that in the fasting animal the liver discharges into the blood stream large quantities (up to 100 grammes per day) of ketone bodies, which are apparently used in the metabolism of the fasting animal, as only a small fraction of these appears in the urine.

The liver apparently is also important in the metabolism of fats. It is well known that the fat concentration in the liver may rise to a high level in certain conditions, and that these fats are more unsaturated than those existing in the general fat depots. It is not possible, however, to say just exactly what part the liver plays in the metabolism of fats. It has been demonstrated by Best[18] that the dietary constituents determine to some extent whether or not the liver will accumulate large deposits of fat. Choline appears to be one of the important substances, and in its absence fatty accumulation takes place in the liver. Dragstedt has shown that there is a substance present in the pancreas which he designates "lipocaic"; the injection of this will cause a resolution of lipoid accumulation in the liver of animals from which the pancreas has been removed. Best, however, considers that this is an accessory food factor, not a hormone.

The relationship of the liver to protein metabolism appears to have three major points of interest. The specific dynamic action of proteins on the basal metabolism is explained by some writers as being due to the amount of work which the liver does on the ingested proteins in deaminizing them, and this appears at the moment to be the most satisfactory explanation of this phenomenon.

The action of the liver in deaminizing amino-acids and turning them out as urea and glucose has already been mentioned; but the third feature is that of the production of blood proteins by the liver.[30] Whipple and his co-workers[31] have confirmed the observations of others, and have demonstrated conclusively that when an animal is bled and the blood proteins have been reduced in amount by the replacing of the corpuscles in saline solution, a large amount of protein can be replaced almost immediately (up to 40% of the total blood proteins in twelve hours); but after these protein "stores" have been depleted by repeated withdrawals over several days, a considerable time is required to build up the blood proteins to normal and this depends on the integrity of the liver; it can therefore be taken for granted that the main source of blood proteins, except globulin, is the liver. Special types of these proteins have recently come under notice, and none more than prothrombin, which is apparently formed by the liver,[32] for in cases of liver deficiency the blood prothrombin content cannot be built up, no matter how much vitamin *K* is given to the animal. That is to say, disease of the liver may result in a low blood prothrombin content in two ways: (*a*) defective absorption of vitamin *K* due to the absence of bile from the intestine, (*b*) defective formation of prothrombin due to disease of the liver. It may be mentioned in passing that evidence indicates the need for absorption of the general fats from the intestine for the absorption of the fat-soluble vitamins; that is, animals taking large quantities of mineral oil by mouth may develop fat-soluble vitamin deficiencies because of the large amounts of vitamin excreted in the unabsorbable oil. This is probably of importance in those cases in which obstruction of the ampulla of Vater results in obstruction of the pancreatic duct, when no matter how great a quantity of bile salts is given by mouth, the fats which have not been subjected to the lipolytic action of the pancreatic juice will not be absorbed. In these cases one of the water-soluble napthaquinone substances will be required to be administered by injection or by mouth.

The Liver and Medicaments.

Another interesting development, so far as the production of blood proteins is concerned, is the demonstration that after the use of gum acacia infusion the reticulo-endothelial system and liver become blocked by the acacia which is taken up into them. The acacia appears to lodge in these cells for a prolonged period, and in association with this condition the animal has a low blood level of proteins, particularly of fibrinogen, over a period of even five or six months.[33]

The liver has two main relationships to medicaments. Many substances used in the treatment of disease are known to be apt to damage the liver. Chloroform and the arsenicals have a particularly bad history in this respect. Accidental ingestion in industry or private life of such substances as phosphorus or carbon tetrachloride also indicates the vulnerability of the liver to substances of widely varying composition. The most important recent research on this subject indicates that the liver is particularly vulnerable to these agents when the carbohydrate supply has been restricted, but even more so when the protein supply is restricted. It has been shown[34] that the liver of dogs becomes extremely vulnerable to chloroform when either protein feeding has been restricted or the dogs' protein sources have been depleted by repeated bleedings. There is evidence that this applies to many of the other substances—for example, arsenicals and selenium[35][36][37]—which cause damage to the liver. Methionine appears to be the most efficacious of the amino-acids, cystine has less protective action, others have none.[38] These findings indicate the obligation of any medical practitioner using hepatotoxic substances to ensure that the patient is receiving an adequate dietary, with a high protein and carbohydrate content, but a low fat content. No experimental work has been done on the question whether the use of a diet rich in protein is protective against the hepatotoxic action of sulphonamides and cinchophen reviewed by Jones.[39]

An interesting point which has come out of experiments on liver damage is that demonstrated by Cameron,[40] that well developed cirrhotic lesions resulting from the administration of carbon tetrachloride may resolve completely, leaving a liver which shows no evidence of any damage. Orr has demonstrated the same phenomenon in cirrhosis caused by butter yellow.[41] This links up with the previous remarks about the reparative processes of the liver. Other papers of importance in relation to cirrhosis are those of György and Goldblatt[42] and Rich and Hamilton,[43] in which it is shown that cirrhosis of the liver may occur as the result of a deficiency in the diet of a substance or substances related to the vitamin *B* type—that is, a substance present in yeast, but not one of the known substances in the vitamin *B* group, and not ascorbic acid. The damage to the liver in cases of exophthalmic goitre[44] bears some resemblance to the lesions described by these authors. It is tempting, in view of Drill and Hays's results,[45] to suggest that they have the same basis, in view of the known deficiency of vitamin B_1 in cases of exophthalmic goitre.

The common statement in text-books is that the liver is the main organ in which detoxication of noxious chemicals takes place. Actually there is very little positive evidence for this statement; this, however, does not necessarily mean that the statement is erroneous. In any discussion of the methods by which detoxication of drugs occurs in the body, there is an assumption that the liver is the most important centre; but it is probable that many other tissues can carry out the processes to some extent.

The action of the liver on drugs[46] is probably best discussed under four headings:

1. It may bind the substance until they are disposed of by other processes; for example, atropine is bound by the liver, but most of it is excreted unchanged in the urine over the following thirty-six hours. The liver binds a large number of other substances and thus keeps the concentration in the blood stream low.

2. The method of detoxication which is most frequently attributed to the liver, but on scanty evidence, is that of conjugating the drug substance with another substance, the resulting compound being inactive on tissues. The addition of glycuronic acid to the fat-soluble substances, camphor, chloral hydrate, ethereal oils, terpenes and some of the sex hormones, gives a compound insoluble in fat and biologically inactive. In the case of the aromatic phenols the main reaction is one of sulphonation; failing this, glycuronic acid compounds are formed. Pelkan and Whipple[47] have shown that sulphonation of phenols occurs mainly in the liver. Acetylation of sulphanilamide has been shown by Van Winkle and Cutting[48] to be carried out mostly by the liver, though the spleen plays some part. Acetylation of sulphapyridine is probably less restricted in its site of occurrence. The other conjugations attributed to the liver are mainly conjugations with amino-acids. Glycine is added to benzoic acid to form hippuric acid. Glutamine, ornithine and cystine have been occasionally

reported in conjugated products. Methylation is reported for pyridine and for selenium and tellurium compounds, demethylation in the case of trimethylamine and purine bases.

3. Only two types of substances are known to be excreted to any extent in the bile; these are hexamethylenetetramine and the tetrahalogen compounds of phenolphthalein.

4. Oxidation and reduction of administered drugs no doubt occur. There is not sufficient evidence to indicate the importance or site of this action.

The relationship of the liver to the destruction of the barbiturates is not known, but there are observations of importance to clinicians using these agents. Cameron and Saram[39] showed that damage to the liver by carbon tetrachloride caused "Pentobarbital Sodium" and "Evipan Sodium" to have on rats a much longer and more intense action than before the damage to the liver. The actions of barbital sodium and phenobarbital sodium were not apparently affected. The objection that the carbon tetrachloride may also have affected the central nervous system was overcome by Scheifley and Higgins,[40] who showed that partial hepatectomy in rats increased the duration and effect of the action of ethyl-o-ethylphenylurea and "Pentobarbital Sodium", but did not apparently alter the action of "Pentothal Sodium". Thus it can be said that liver damage alters the duration and intensity of the actions of some, but not all, of the short-term barbiturates, and does not affect the action of the two long-term barbiturates which have been investigated.

From time to time there appear papers on tests for liver function. They are concerned with the ability of the liver to alter an administered substance (for example, the hippuric acid test[41]) or to excrete administered substances (for example, the phenolphthalein test), or to use up administered material (for example, the lævulose tolerance test). There are also suggestions that the physical state or the quantity[34] of various blood proteins may be used as a test of liver function. So far, all of these tests appear to give an indication of liver damage only when the liver is extensively damaged. It would appear, however,[42] that the hippuric acid excretion after administration of sodium benzoate and the blood content of prothrombin as determined by the two-stage methods may be the tests giving the best indication of the degree of liver damage. Magath[42] has shown that the Takata-Ara test is neither specific for liver damage nor sensitive in cases of liver damage.

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THE TUBERCULIN PATCH TEST.

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DURING the past twelve months an investigation has been in progress into the reliability and usefulness of the Australian-made tuberculin patch test, particularly in comparison with the standard intracutaneous test of Mantoux. Military service will probably postpone the completion of this investigation; but it is considered justifiable at this stage to present a preliminary report, as the test promises to play a rapidly increasing part in the diagnosis of tuberculosis, more especially in children.

By way of introduction it will be profitable to review briefly the various tuberculin tests which have been advocated in the past. The most extensive report yet published on this subject was compiled for the Medical Research Council of the Privy Council in 1932 by D'Arcy Hart,[(1)] who stated that the test chosen "should as far as possible . . . be safe, easily performed, capable of quantitative application, sufficiently sensitive to detect every tubercle-infected individual, and reliable in the diagnosis of clinical tuberculosis". The value of each particular test may be considered according to this standard.

Review of Other Tuberculin Tests.

After a subject has been infected with the *Mycobacterium tuberculosis* a change occurs in the reaction of his tissues to this organism and its metabolic products. This changed tissue reaction, or allergic response, is known as Koch's phenomenon. It was first used clinically in 1890 in the subcutaneous test for tuberculous infection which was described by Koch himself. Since then many tuberculin tests have been described, but only a few of them need be discussed here. They differ mainly in the method of administration of the tuberculin, and accordingly may be classified into conjunctival, subcutaneous, cutaneous, percutaneous and intracutaneous tests. The first two of these tests have now fallen into disuse because of the subsequent discovery of other tests which are less dangerous and more reliable. The percutaneous test was introduced by Moro in 1907, and is still popular in Scandinavian countries. It is performed by rubbing an ointment containing equal parts of old tuberculin and anhydrous wool fat into the skin of the chest or abdomen. An efflorescence of papules constitutes a positive response; but a considerable proportion of clinically tuberculous patients fail to react. The sensitivity of the test is increased if the skin is previously cleansed and defatted with ether; but the error (15% to 20%) is still too great for the test to be of much practical value. It will be mentioned later, however, in connexion with the patch test.

In the last three decades the tests which have been most widely used are the cutaneous test described in 1907 by von Pirquet, and the intracutaneous test described in 1908 by Mantoux in France and by Mendel in Germany. These two tests have been exhaustively compared, and it has been shown beyond doubt that the Mantoux test is at least 10% more sensitive than that of von Pirquet. The latter also has the disadvantages that only one strength of tuberculin can be used and that the volume of tuberculin entering the skin cannot be measured or regulated. In fact, the great majority of workers would agree with the statement that the Mantoux test is preferable to all others previously described, being more sensitive, more reliable and on the whole more convenient.

Disadvantages of the Mantoux Test.

No biological test, however, is absolutely reliable. Certainly the Mantoux test cannot reasonably be regarded as the ideal infallible tuberculin test. What, then, are its limitations and its drawbacks? Let us consider it in the light of D'Arcy Hart's description of the ideal test. The first of the five qualities required is safety, in which respect the Mantoux test is admittedly better than most of the earlier tests. But it does involve an injection, with attendant trauma and danger of infection; it often produces pyrexia when active tuberculosis is present, sometimes severe local necrosis, and rarely sloughing; and focal reactions are not infrequent, occasionally with serious results, as Lincoln and Grethmann[(2)] have recently shown. Some of these by-effects appear to be less frequent if the test is performed with Seibert's purified protein derivative of tuberculin instead of old tuberculin (Anderson[(3)]); but I have no experience of this substance, which is rather costly.

It is particularly in respect of simplicity or ease of application, however, that the Mantoux test falls short of the ideal. The technique requires a certain amount of skill if errors are to be avoided; it also requires special syringes (preferably one for each dilution of tuberculin) with short bevel needles, and means of sterilization, potent, fresh, sterile tuberculin accurately diluted, and suitable control fluid. In addition, the test absorbs the time of the physician or other skilled person on two, or often three, days, and a judicious psychological approach to the patient is essential, with a nurse or assistant to hold the younger children. This is particularly necessary in carrying out mass surveys of children, in some of whom the fear of the needle may precipitate hysterical outbursts, especially when the test has to be repeated with a higher strength (Pearse, Fried and Glover[(4)]).

The Mantoux test is reasonably suitable for quantitative testing; but its sensitivity in detecting tubercle-infected persons is not infallible. There is no response during the incubation period, the duration of which is usually three to seven weeks, but may extend to several months; and in infants radiological signs of the disease may precede the obtaining of a positive Mantoux reaction (Rosenberg and Levine[(5)]). Certain types of tuberculous infection frequently fail to cause a reaction—notably miliary and meningeal infections, any advanced infection with severe toxæmia, and tuberculosis of serous membranes. Also non-reactivity may develop during tuberculin therapy and is reported to occur during measles and vaccinia and possibly even after ultra-violet ray treatment.

These same deficiencies may be quoted in answer to the question: Is the Mantoux test reliable in the diagnosis of clinical tuberculosis? D'Arcy Hart's series of 1,030 patients of all ages showed 96% to react to the standard dose of 0·1 cubic centimetre of old tuberculin in a dilution of 1 in 1,000, 97·25% to react to 1 in 100 strength, and 97·7% to react to 1 in 10 strength. The more recent figures of Musacchio[(6)] and others show percentages slightly lower than these. It must also be borne in mind that the error or proportion of non-reactors would be relatively greater in the youngest age group of 0 to 5 years—that is, in the period when the tuberculin test is most often required. In addition, pseudo-reactions (atypical non-specific reactions) occur with the higher strengths of old tuberculin and even occasionally with a dilution of 1 in 1,000, adding to the not infrequent doubtful cases in which the interpretation of the reaction is difficult.

So although the Mantoux test is the most accurate of the skin tuberculin tests and has proved to be extremely valuable in pædiatric practice, we must not close our eyes to its imperfections. It will be seen that the patch test overcomes some of these difficulties, particularly as regards safety and ease of application.

The Patch Test.

The patch test is a percutaneous method of detecting allergy to tuberculin, like the inunction test of Moro from which it has developed. Moro's test was improved by the use of a fat-solvent for cleansing the skin (Widowitz, 1922), by concentration of the tuberculin (Moro, Hamburger), and by the use of a tuberculin plaster which dispensed with the need for friction (Malmberg and Fromm, 1931,[(7)] Wolff, 1933[(8)]). But even

[1] Read at a meeting of the Melbourne Pædiatric Society, August 13, 1941.

[2] Work done with the aid of a grant from the University of Melbourne Tuberculosis Research Fund.

with these variations, the reliability of the test is little better than that of the von Pirquet test, which has an error of 10% to 15%. In 1933 Grozin[9] used a patch made by placing "one or two drops of original old tuberculin (Koch) on a piece of adhesive plaster". Such a test has great technical advantages; but it was shown to be only 96% as accurate as the von Pirquet test.

Finally Hermann Vollmer[10] found that filter paper saturated with tuberculin and strapped to the skin would give satisfactory reactions. He began his work in Germany in 1930, but was afterwards appointed to the Mount Sinai Hospital, New York, from which all his results have been published. Briefly, Vollmer's figures[10,11,12,13] show that his patch test is, if anything, even more reliable than the standard Mantoux test performed either with 0·1 cubic centimetre of old tuberculin (1 in 1,000) or with the customary first strength dose (0·00002 milligramme) of Seibert's purified protein derivative of tuberculin. The Lederle Laboratories in the United States of America manufactured these patches and put them on the market late in 1937, and shortly afterwards they were also being made by the firm of Allen and Hanburys, Limited, in England.

In Dr. Donald Paterson's wards in the Hospital for Sick Children, Great Ormond Street, London, I had the opportunity during 1938 and 1939 of using both makes of patches, confirming the good results of Vollmer in America and of Dudley Hart[14] and Court[15] in England. I brought back to Australia a packet of the British patches, but was disappointed to find on using them on out-patients at the Melbourne Children's Hospital that the results were inferior to those obtained at Great Ormond Street. Possibly the four or five weeks' exposure to tropical conditions *en route* had affected the potency of the tuberculin. The possibility of manufacturing similar patches in Australia was naturally considered next, and Dr. F. T. Wheatland, of the Commonwealth Serum Laboratories, readily undertook their preparation for clinical trial. I am greatly indebted to him for his encouraging advice and for kindly supplying me with the patches used in this investigation.

The method of preparation used has been that advocated by Dr. Douglas Anderson,[16] of Sydney, to whom much credit and gratitude are due for his carrying out of the somewhat tedious preliminary experimental work. Briefly, disks of thin filter paper of an area of one square centimetre are saturated with undiluted tuberculin produced from Seibert's synthetic medium and dried in a dust-free chamber. This procedure is then repeated, and when the disks have been dried the second time they are placed on a strip of waterproof adhesive strapping. The strapping is cut into pieces two inches by one inch in area, each containing two filter paper disks placed about one inch apart. The adhesive surface is then protected with crinoline gauze and the whole patch is enclosed in a sealed "Cellophane" envelope.

The Technique.—A hairless cutaneous area over the chest, along the medial aspect of the arm or in the interscapular region, is cleansed and "defatted" with ether, acetone or benzene, and allowed to dry. (Alcohol is unsatisfactory unless it is used liberally, with scrubbing, and unless adequate time is allowed for it to dry thoroughly before the patch is applied.) The crinoline is removed from the strapping and the patch is applied to the "defatted" area, adhesion being assured by pressure with the warm palm of the hand. Most workers do not allow bathing while the patch is in position; but if good waterproof strapping is used and firmly applied, it is probably necessary to prohibit only very hot baths and vigorous sweat-producing exercise. The patch is removed after forty-eight hours, and the reaction is read in seventy-two or ninety-six hours, preferably the latter. The dried tuberculin in the filter paper is liquefied by the insensible perspiration of the skin and gradually absorbed. The reaction may be already present when the patch is removed, though its maximum intensity is usually attained twenty-four to forty-eight hours later. It is more or less sharply confined to the area that was in contact with the tuberculin-treated filter paper, and in positive cases consists of various degrees of erythema and induration with papules and vesicles. In the grading of reactions the classification used in this investigation has been adapted from that of Vollmer (Table I and Figure I).

TABLE I.
Classification of Reactions to Mantoux and Patch Tests.

Mantoux (Aronson).	Grade.	Patch. (*After* Vollmer.)
Erythema and a trace of œdema, less than 5 millimetres in diameter.	±	Faint erythema ± solitary pinhead papule.
Erythema, œdema 5 to 10 millimetres in diameter.	+	Erythema with few (up to 6 or 8) lichenoid papules.
Erythema, œdema 11 to 20 millimetres in diameter.	++	Many lichenoid - follicular papules, slight induration.
Erythema, œdema more than 20 millimetres in diameter.	+++	Confluent eruption (papules and tiny vesicles) with marked induration.
Marked erythema and œdema with necrosis.	++++	Blister formation with spread beyond disk area.

The Present Investigation.

The patch test performed with Commonwealth Serum Laboratories' patches has been compared with the standard Mantoux test in a total of 240 persons, distributed in age groups as follows: up to six years, 84 cases; seven to twelve years, 100 cases; thirteen to twenty years, 35 cases; twenty-one years and over, 21 cases. The subjects were drawn from the Melbourne Children's Hospital (110: 64 in-patients, 46 out-patients), from the Frankston Orthopædic Section of the Children's Hospital (78), from the Austin Hospital (27), from the Royal Melbourne Hospital (16), and from private practice (9). The Mantoux test was performed in each case by myself with the Commonwealth Serum Laboratories' old tuberculin (human strains), 0·1 cubic centimetre of a dilution of 1 in 1,000, which was never more than three weeks old. The patch test was applied the same day. The site for the latter was usually the front of the chest; but for toddlers and mischievous subjects

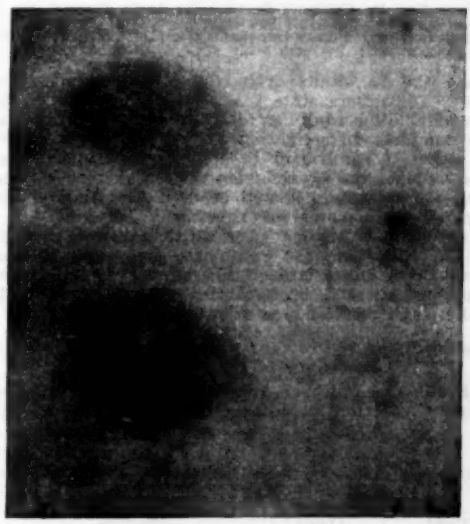

FIGURE I.

the interscapular region was chosen, and in all except the earlier cases exposed areas were not used. Bathing or wetting of the patch was avoided. After forty-eight hours the reaction to the Mantoux test was read and the patch was removed. After seventy-two to ninety-six hours the patch reaction was read, and if none was present the ward sister was asked to report any delayed reaction.

In the first forty cases the patches used contained only one disk of tuberculin-treated filter paper; subsequently two disks were used in each patch. It was found in these later cases that occasionally there was considerable disparity between the reactions to these two disks, and in

three cases (about 1·5%) one disk produced no reaction, although the other elicited a weak ("+") reaction. Whether these irregularities are due to faulty cleansing of the skin, to uneven distribution of tuberculin through the filter paper, or to some other cause, their occasional occurrence is certainly an indication for the use of patches which contain not less than two disks or squares. A control piece of filter paper was included in the original old tuberculin patches used by Vollmer, but none was used in this investigation, as it is now generally considered unnecessary, since all non-specific reactions fade before the true tuberculin reaction has reached its height. The so-called "control" included in certain proprietary patches is not a true control at all, being made with glycerin broth, whereas the tuberculin used is prepared on Seibert's synthetic medium.

The results of this investigation (Table II) show that there was complete agreement between the two tests in 229 cases out of a total of 240. Nine children and one adult reacted to the Mantoux test and did not react to the patch test, while one child failed to react to the Mantoux test and reacted to the patch test. It is reasonable, however, to separate the 21 adults from the others, because Grant Taylor[17] and others state that the patch test is probably not as reliable for adults as for children, and unfortunately this incomplete investigation does not include sufficient cases either to confirm or to disprove this idea. Now if for the moment the figures from the Frankston Orthopædic Section are set aside, it will be seen that the remaining 141 cases show complete agreement between the two tests except for the one case which favoured the patch test. In this case the radiologist reported pulmonary shadows "very suggestive of tuberculosis" even before the tuberculin tests had been carried out, so it is unlikely that the patch reaction was a "false positive".

TABLE II.

Comparison of Results of the Mantoux and Patch Tests.

Type of Reaction.	Subjects Aged 0 to 20 Years.		Subjects Aged Over 20 Years.	Totals.
	Group I.[1]	Group II.[2]		
M+ P+[3]	56	42	16	120
M− P−	84	21	4	109
M+ P−	0	9	1	10
M− P+	1	0	0	1
Totals ..	141	78	21	240

[1] Subjects from the Children's Hospital, the Austin Hospital, the Royal Melbourne Hospital and private practice.
[2] Subjects from the Frankston Orthopædic Section of the Children's Hospital.
[3] M = Mantoux test; P = patch test.

Possible Effect of Previous Exposure of the Skin on its Reactivity to the Patch Test.

At Frankston, however, the patch test failed to produce a positive reaction in nine cases out of 78, or 11·6%. An error of this magnitude suggested that there must be some local cause to account for it. A closer study of these nine cases was therefore made (Table III) and the facts suggested that the repeated exposure to fresh air, wind and sunshine, which is part of the routine treatment at Frankston, may have so affected the texture of the skin of these children that absorption of the tuberculin was hindered. Vollmer[12] mentions extreme cold, myxœdema and ichthyosis as likely to produce a similar interference with absorption.

The conclusion that previous exposure to the elements will retard or prevent the skin reaction to the patch test is based on the following facts.

1. In this investigation, out of 130 positive reactors to the standard Mantoux test, the only ones who failed to react to the patch test were nine in-patients of the Frankston Orthopædic Section and one man, aged fifty-two years, who had led an outdoor life.

2. Detailed quantitative analysis of the intensity of the reactions in all Frankston patients, as measured in *plus* signs, shows a discrepancy between the reactions to the intracutaneous and to the percutaneous tests, which is minimal on admission to hospital, but which increases with the patient's length of stay in that hospital (Table IV), and it is true that the amount of exposure in these cases is roughly proportional to the length of stay. Moreover, in the majority of the Frankston cases a special endeavour was made to choose a site which had had minimal exposure to the elements. Had all the patches been applied, say, to the upper sternal region, it is reasonable to assume that the results would have shown an even greater discrepancy with increasing length of stay at Frankston.

TABLE IV.

Does Degree of Exposure to Elements (as Indicated by Duration of Patient's Stay at Frankston Orthopædic Section) Affect Reaction to the Patch Test over Exposed Areas?

Number of Patients.	Length of Stay at Frankston. (Years.)	Intensity of Reaction. (Sum Total of *Plus* Signs.)		Sum Total "Patch +" Signs in Proportion to "Mantoux +" Signs.
		To Mantoux Test.	To Patch Test.	
108	0 (Children's Hospital patients)	76½	72	94%
16	Less than 1	27	18½	73%
19	1	28	16½	59%
11	2	22	12½	57%
20	3 or more	52	30½	59%

3. In three cases patches were applied simultaneously on a sunburnt area and on a relatively unexposed part. In each case the latter area showed the greater reaction, and the sum totals of the reactions were in the ratio of 3:1.

4. In the literature appear reports from America by Peck and Wegman[13] and by Fineman and Bair,[14] showing unsatisfactory results with the Vollmer patch test. In

TABLE III.

An Analysis of the Data Relating to Nine Patients at Frankston who Reacted to the Mantoux Test but Failed to React to the Patch Test.

Patient.	Age. (Years.)	Diagnosis.	Years at Frankston.	Site of Patch.	Comment.
J.C.	8	Tuberculous spine.	4	Axilla.	P[1]±; S[2]++; TT.[3]
N.B.	4	Tuberculous spine.	3	Leg.	S++.
R.C.	7	Tuberculous knee.	2	Axilla.	TT; dry skin, cracked lips.
C.R.	5	Multiple bone tuberculosis.	3	Chest.	S++.
M.O'B.	14	? Tuberculous hip; ? osteomyelitis.	2½	Chest.	S+; ? non-tuberculous.
M.G.	6	Tuberculous knee.	5	Chest.	Single disk; S+; P++ nine months later.
A.D.-G. ..	13	Tuberculous spine.	1½	Axilla.	Single disk; S++; dry hair and skin; P+ nine months later.
A.C.	10	*Coxa protrusa*	4/12	Leg.	S++; clinically non-tuberculous.
K.J.	8	Multiple chronic osteomyelitis.	1	Chest.	Single disk; clinically non-tuberculous.

[1] P = reaction to patch test. [2] S = pigmentation from sunburn. [3] TT = recent tuberculin therapy.

each of these investigations the patches were applied below the elbow, an area in children where the skin is invariably subjected to considerable exposure, particularly in Negroes, who formed 50% of the subjects in these investigations. And in 1926 Morabito[20] showed that after ultra-violet ray treatment the cutaneous or von Pirquet test may fail to produce a reaction. Theoretically, the patch test, depending on percutaneous absorption, would be even more likely to be so affected.

The evidence therefore supports the idea that exposure to the elements can interfere with the reaction to a percutaneous test by affecting the texture of the skin; but obviously further work is necessary to confirm this. This factor, however, appears to be eliminated readily in the ordinary case by the choice of a suitable site for application of the patch.

Does the Patch Test Miss any Children with Active Tuberculous Lesions?

It is in the cases of incipient and active tuberculosis that detection by tuberculin tests is so desirable. The important question is: Does the patch test miss any patients with active tuberculosis, and if so, how does it compare with the Mantoux test in such cases? Table V shows that of 114 patients with clinical, radiological or bacteriological findings suggestive of tuberculous infection, 111 (97·4%) were detected by one or other of the tuberculin tests, while three were apparently anergic. (One had miliary and one meningeal tuberculosis; one had unproven Pott's disease.) The previously discussed group of children from Frankston who failed to react to the patch test appear again and tend to give a false impression of the reliability of the patch test in general; but the 58 tuberculous patients from other hospitals show the patch test to be, if anything, even more sensitive than the standard Mantoux test.

TABLE V.

Proportion of Patients with Clinical, X-ray or Bacteriological Findings Suggestive of Tuberculous Infection who were Detected by Mantoux and Patch Tests (0 to 10 Years Age Group).

Number of Patients with Tuberculous Infection.	M+ P+	M+ P−	M− P+	M− P−	Comment.
56	48	7[1]	—	1[4]	Frankston.
35	30	—	3[3]	2[4]	Children's Hospital.
21	21	—	—	—	Austin Hospital.
2	2	—	—	—	Royal Melbourne Hospital and private practice.
114	101	7	3	3	

[1] See text.
[2] ? Pott's disease.
[3] Mantoux reaction with 1/200, +; with 1/1,000 ?.
[4] One with miliary and one with meningeal tuberculosis.

The Results of Other Investigations.

The present comparative study of the Mantoux test and the Vollmer-type patch test has dealt with a relatively small number of cases; but the results to date are in accord with those obtained by the great majority of other workers. Vollmer,[13] in his latest paper, added his own figures to the summarized results of ten other investigations, totalling more than 6,000 cases, and showed that the patch test is less than 1% behind the Mantoux test in regard to sensitivity. More recently Kereszturi[21] made a survey of 19 publications on the subject; but she excluded the results of certain studies as being not suitable for general appraisal, and utilized the remainder to arrive at the unwarranted conclusion that the patch test has an error of about 15%. In compiling their summaries of the literature, both these authors, particularly Kereszturi, have actually pooled together various series of figures which in many cases are not strictly comparable. For instance, some workers compared the patch test with the Mantoux test carried out with dilutions of 1 in 10,000 or 1 in 1,000 or 1 in 100 or even 1 in 10; others for the Mantoux test used Seibert's purified protein derivative of tuberculin in various strengths; and others compared the patch with the von Pirquet test. Then again in some studies the patches were saturated with old tuberculin and in others with synthetic medium tuberculin, though this variation seems to make little difference. Obviously no statistical value can be attached to any summary unless it includes only those studies in which comparable methods and conditions obtained. If consideration is given only to those figures obtained by a comparison of the Vollmer-type tuberculin patch test with the small standard Mantoux test (0·1 cubic centimetre of old tuberculin, 1 in 1,000), as has been done in the present investigation, the inevitable conclusion is that the patch test is at least as sensitive as the Mantoux test, and possibly slightly more so (Table VI). Other workers, such as Leonidoff,[22] Craig and Scheuer,[23] and Pearse, Fried and Glover,[4] have apparently shown that the patch test is also more sensitive than the Mantoux test when this test is performed with the customary first strength dose of Seibert's purified protein derivative. The results obtained by Peck and Wegman[13] alone are widely at variance with those of all other workers, and one feels, with Vollmer, that such a discrepancy as they report could be due only to technical factors—for example, an unsuitable site for the patch, inadequate adhesion, stricter criteria for regarding a reaction as positive *et cetera*. The conclusion is justified that the Vollmer-Lederle patch test is fully as sensitive as the Mantoux test and could perfectly well replace it in pædiatric practice.

TABLE VI.

Results of Comparative Studies of the Vollmer Patch Test with the Standard Mantoux Test (0·1 Cubic Centimetre of Old Tuberculin, 1 : 1,000).

Author.	Total Number of Cases.	Positive Patch Reactions.	Reactors to Mantoux Test.	Remarks.
Vollmer[13] ..	666	42	41	New York, 1937–1940.
Steward[24] ..	96	96	90	Tennessee, 1938.
Taylor[17] ..	744	218	206	N. Carolina, 1939.
Saul[25] ..	25	25	23	U.S.A.
Greenwald[26] ..	404	16	16	U.S.A.
[1] Dudley Hart[14]	536	97	96	London, 1938.
[1] Court[14] ..	210	129	131	London, 1939.
Total ..	2,681	623	603	
Colebatch ..	219	105	113	Melbourne, 1941.
Total ..	2,900	728	716	Commonwealth Serum Laboratories' patches.

[1] The criteria which these two authors used for reading a Mantoux reaction as positive differ from the accepted classification of Aronson and the National Tuberculosis Association; but the practical results would scarcely be affected.

A Comparison of the Vollmer-Lederle and the Commonwealth Serum Laboratories' Patches.

That the patches prepared by the Commonwealth Serum Laboratories are just as reliable as the Vollmer-Lederle patches is suggested by the results obtained with the former in this investigation (see Table II). To prove this, a box of Vollmer-Lederle patches was imported from America and the reactions to them were compared with the reactions to Commonwealth Serum Laboratories' patches simultaneously applied to 70 subjects (Table VII). Sixty-four of the 70 patients gave corresponding results, while six (8·6%) failed to react to the Vollmer-Lederle patches and reacted to the Commonwealth Serum Labora-

TABLE VII.

Comparison of the Reactions to the Vollmer-Lederle and the Commonwealth Serum Laboratories' Patches.[1]

Age Group. (Years.)	C.S.L. + V.L. +	C.S.L. − V.L. −	C.S.L. + V.L. −	C.S.L. − V.L. +
0 to 20	44	16	6	0
Over 20	3	1	0	0
Total	47	17	6	0

[1] The sum total of the reactions in *plus* signs: Commonwealth Serum Laboratories' patches = 114, Vollmer-Lederle patches = 81.

tories' patches. And the sum total of the *plus* signs in the Commonwealth Serum Laboratories' patch reactions was 114, compared with 81 in the Vollmer-Lederle reactions. If these figures were accepted unconditionally, the interpretation would be that the Commonwealth Serum Laboratories' patches were superior in sensitivity to the Vollmer-Lederle patches. It is more probable, however, that the latter had deteriorated in potency as a result of their passage through the warm, humid atmosphere of the tropics. The dried synthetic-medium tuberculin in the patches is said to retain its potency almost indefinitely at ordinary temperatures; but it is possible that the "Cellophane" envelopes may not remain air-tight in tropical heat, and in that case the humidity may affect the patches. Further work is required to determine the stability of the patches under varying climatic conditions; but it is generally considered that under ordinary conditions they will remain potent for at least one year. None of the Commonwealth Serum Laboratories' patches supplied for this investigation was more than four months old when used.

Advantages and Disadvantages of the Patch Test.

The reliability of the test having been proved, one can next consider its advantages, which are chiefly concerned with its safety and ease of application.

1. It is painless, even the severe reactions producing only pruritus or a burning feeling. It is therefore acceptable even to nervous children. (In highly allergic subjects these symptoms may be readily avoided, if it is so desired, by removing the patch after only twenty-four hours' application. If no reaction occurs, the test may then be repeated with forty-eight hours' application.)
2. There is no trauma to the skin through injection or scarification, and no danger of infection.
3. There is no need for instruments or means of sterilization.
4. No assistant is required, and it demands the minimum of manipulative skill and so can be applied by a nurse or an untrained person.
5. It is less time-consuming than the Mantoux test.
6. The reaction is confined to a sharply limited area, with less than 1% of subjects showing any blister formation.
7. Reactions are on the whole easier to interpret than the Mantoux reactions, and pseudo-reactions are almost unknown. (Taylor[37] and other authors also states that the patch test is read as easily in Negroes and Indians as in whites; but in the one tuberculous aboriginal child available for the present investigation the positive reaction was not so clearly legible as is usual in whites.)
8. Focal and constitutional reactions practically never occur, even when two or more patches are applied simultaneously.

Naturally, good results are obtained only by careful attention to the details of the technique, especially the choice of a suitable site, adequate "defatting" of the skin, and good adhesion to seal the patch effectively. The prohibition of bathing may seem an inconvenience at times, but this is probably an unnecessary restriction. The only real disadvantage in the patch test is that the degree and rate of absorption of the contained tuberculin do vary to some extent with atmospheric conditions and with the natural moisture of the skin, although Vollmer considers that forty-eight hours' close contact guarantees adequate absorption. It should in fairness be added that, in its sensitivity in detecting tubercle-infected persons, the patch test is liable to the same defects as may be shown by the standard Mantoux test (see "Disadvantages of the Mantoux Test").

Quantitative Application of the Patch Test.

The quantitative application of the test is still in the experimental stage, and although it furnishes a means of estimating the degree of allergic response to tuberculin up to a certain point, it does not seem likely to have as wide a range of usefulness as the Mantoux test. Goldberger[27] showed that if the Mantoux test produces a reaction with old tuberculin, 1 in 10,000, then the patch test will produce a positive reaction after only twenty-four hours' application; if the Mantoux test produces a reaction with a dilution of 1 in 100,000, the patch test will produce a reaction after twelve to eighteen hours; and if the Mantoux test produces a reaction with a dilution of 1 in 1,000,000, the patch test will produce a reaction after three to twelve hours. (I have obtained a positive patch reaction after only six hours' application.) Vollmer, Zelson and Rubin[40] reported similar results with an allergometric patch test, in which the adhesive strip contains five small filter paper patches saturated with decreasing concentrations of tuberculin. However, more work is required to show whether, by prolonging the period of contact beyond forty-eight hours or by some other means, it is possible to produce reactions comparable with those obtained from dilutions of 1 in 100 and 1 in 10 with the Mantoux test.

Conclusion.

Though there are some matters concerning the patch test which require further investigation, one may at this stage conclude that the filter paper type of tuberculin patch test (as distinct from the various tuberculin ointment patch tests) has withstood the test of several years' clinical trial and has proved a satisfactory method for the preliminary tuberculin testing of children. If no reaction is obtained, it is advisable in cases in which tuberculosis is suspected to proceed with the Mantoux test with old tuberculin (1 in 100), just as one would after a negative response to the standard Mantoux test. In Vollmer's own words: "The patch test does not meet with the rigid requirements of statisticians who wish to discover the greatest possible number of positive reactors, even though some of the reactions prove to be pseudo-reactions which merely cause anxiety and unnecessary expense. The patch test does claim to make tuberculin testing a simple, innocuous and generally acceptable procedure, which reliably discovers all cases worth singling out for isolation, treatment or observation."

Summary.

1. An investigation has been undertaken into the reliability and clinical application of the Vollmer-type tuberculin patch test with patches prepared by the Commonwealth Serum Laboratories, Melbourne.
2. A critical review of previously described tuberculin tests is presented, indicating that the intracutaneous test of Mantoux is the most accurate, but that it has many drawbacks.
3. The development of the percutaneous method of tuberculin testing is traced from the inunction test of Moro up to the present Vollmer-type patch test, with a description of the technique employed.
4. A comparative study of the patch test with Commonwealth Serum Laboratories' patches and the standard Mantoux test has been made in 240 cases. In children the patch test proved equally as reliable as the Mantoux test, except in nine cases from an orthopædic hospital.
5. From detailed study of these nine cases it is suggested that repeated exposure to the elements (which is part of the routine treatment) has altered the texture of the skin of these children, and so interfered with the absorption of the patch tuberculin. Certain evidence is presented which strongly supports this theory.
6. The results of the present investigation are in accord with those of the great majority of other workers, justifying the conclusion that the Vollmer-type patch test is fully as sensitive as the standard Mantoux test in children and may safely replace it in routine preliminary testing.
7. The Commonwealth Serum Laboratories' patches have been shown to be equally as reliable as the Vollmer-Lederle patches. But it is suggested that imported patches may deteriorate during transit through the tropics.
8. The advantages and disadvantages of the test are described, and it is shown to be well suited for use in mass surveys, in routine hospital work, and particularly in private practice.
9. Directions are indicated in which further work is required, such as the stability of the patches, the effect of previous skin exposure on the absorption of tuberculin, and the quantitative application of the test.

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THE PATCH TEST: A SIMPLE TUBERCULIN TEST FOR GENERAL MEDICAL PRACTICE.[1]

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THE specific allergic reaction to tuberculin in those who have been infected with the tubercle bacillus may be elicited in a number of ways, nearly all of which have had their vogue in clinical medicine. Tuberculin has even been dropped into the human eye! For more than thirty years experimenters have striven to simplify the test, but to apply it in such a way that a reaction is elicited from every allergic subject, yet so that no inconveniently sharp reactions are produced in the very sensitive.

The intracutaneous test of Mantoux has now come to be recognized by nearly all who are interested in the subject as best fulfilling the requirements of simplicity, sensitivity, uniformity and ease of application. In 1938 a method of applying the Mantoux test employing but a single injection was devised;[15] its use for some thousands of tests has shown that it detects all or nearly all potential reactors with few inconveniently sharp reactions, and that it is adequate for most practical purposes. But the Mantoux test, however simplified, has disadvantages that often stand in the way of its application to occasional patients in general medical practice. Dilutions of tuberculin have to be made and they do not keep for long, although the use in Denmark recently of quinosol instead of phenol as an antiseptic for tuberculin solutions appears to show that great improvement is possible in this direction. Tablets and "dry dilutions" of the purified protein derivative of tuberculin are still rather costly for occasional use, and again, dilutions of these containing phenol are unstable.

It is the purpose of this paper to draw attention to the evolution of the percutaneous tuberculin test and the present position of its most recent development, the patch test; also to describe experiments made in an endeavour to improve on the tuberculin patches in use hitherto; and finally to describe a simple and inexpensive method of making tuberculin patches suitable for use in general medical practice.

Historical.

The first percutaneous test was the Moro-Doganoff test,[28] which was described in 1907, and thus by a year or so antedated the Mantoux test; a tuberculin ointment in an anhydrous wool fat base was rubbed into the skin with a finger stall, but the test proved too insensitive for general use. Improvements in the ointment and improvements in the finger-stall method followed, and improvements are still being made. In 1908 Lautier[29] hit on the idea of applying a drop of tuberculin to sticking plaster, allowing it to dry in air and applying the plaster to the skin. The insensible perspiration was supposed to effect solution of sufficient tuberculin for some to enter the follicles of the skin and set up the tuberculin reaction. But this method had various physical disadvantages (for instance, the drop of tuberculin would spread out irregularly) and the idea was dropped. It was revived in 1930 by Vollmer, and in 1931 Malmberg and Fromm actually mixed the tuberculin with the adhesive coat of the plaster and used a control plaster without tuberculin. In 1937 Vollmer devised a new method.[30] According to his description, thin filter paper was saturated with tuberculin and allowed to dry by hanging in a dust-free room; the paper was then cut into small squares, which were placed on pieces of adhesive tape with forceps. A square of filter paper which had been soaked in *bouillon* was also placed on the adhesive tape as a control. From all accounts Vollmer's patch test has proved satisfactory and it is on the market in America and Europe.

[1] Work done in 1939 with the aid of a grant from the National Health and Medical Research Council. From the Royal North Shore Hospital of Sydney Institute of Medical Research.

Some Unsuccessful Experiments and the Lessons Learned from them.

When Vollmer published his method the present author attempted to copy him, and it was at once apparent that by his method it was very simple to produce tuberculin patches at a low cost in materials. But numerous checks were encountered; difficulties were met with in the preparation of patches, and many batches were found unsatisfactory on clinical trial. It may be useful to set out some of the difficulties met with and the manner in which they have been overcome.

The first check occurred when it was found that filter paper saturated with old tuberculin and hung in a dust-free room would not dry in humid weather owing to the capacity of the glycerin contained in it to absorb moisture. When the paper was dried in the sun the patches made from it were found to be quite impotent. The reason for this is not clear; it is suggested that the tuberculo-protein may have been denatured by the light. In the next experiment the paper was dried in a desiccator and the patches made from it possessed some potency, but failed to elicit reactions in a large proportion of reactors to the Mantoux test.

It was also found that owing to the moisture-absorbing capacity of the glycerin contained in them, the patches soon became damp in humid weather. This has also been observed in tuberculin patches brought to this country from America; in these some of the tuberculin may sometimes be seen to have soaked into the gauze used to cover the adhesive surface of the tape despite the fact that each patch is packed in a little "Cellophane" envelope. To overcome this, adhesive tape of the waterproof variety has been used. Reels of tape one inch wide and a yard long were obtained, the reel was unwound, thirty-six patches were applied at intervals of one inch, and the tape was wound on the reel again. It was not convenient to cover the adhesive surface with gauze, and this was found to be unnecessary. Each patch was cut off from the reel as required for use. It was found that the use of the waterproof strapping enabled the subjects to wash or bathe during the time that the patch was applied.

The next experiments were directed to the production of patches of greater potency. Various thicknesses of paper were tried, but with no better result. Then the saturated and dried paper of the original quality was resaturated with more tuberculin and again dried, and the process was repeated till the paper was supersaturated and looked as if varnished. Again, tuberculin was concentrated to one-half of its volume and the very viscous product was applied to the paper, which was dried in a current of warm air and placed on the adhesive tape before it became damp. The patches made by either of these methods were more potent than those previously produced, but very hydrophile, and the tuberculin came off on the waterproof face of the tape apposed to it on the reel.

A number of different kinds of patches were prepared from absorbent paper impregnated with ointments made up of tuberculin, kaolin and various bases. It was thought that the absorbent paper, by preventing the ointment from "running", would remove one of the principal disadvantages of the tuberculin ointment patch test of Wolff and Hurwitz.[65] But it was difficult to make the patches uniform and they were not very potent.

It was thought that synthetic-medium old tuberculin, such as is used for the preparation of the purified protein derivative of tuberculin, might present advantages over old tuberculin in the preparation of patches, in that the smaller content of glycerin would facilitate concentration and drying, while the absence of foreign protein in the medium might enable control patches to be dispensed with. In 1938 Vollmer and Goldberger published a further small paper,[66] stating that they had been using a tuberculin produced from a synthetic medium for their patches for over a year. Accordingly patches were prepared from paper saturated with a synthetic-medium old tuberculin obtained from the Commonwealth Serum Laboratories.

It was found that filter paper saturated with this tuberculin dried readily; but when disks of filter paper were dried in a desiccator evaporation of moisture occurred more rapidly at the circumference than in the centre, so that migration of tuberculin towards the circumference occurred during the drying, and hence there was a greater deposition of tuberculin at the circumference than in the centre. This was overcome by cutting the paper into strips before saturating it with tuberculin. It has been found advantageous when the paper has been once dried to resaturate it and dry it again.

A Method of Making Tuberculin Patches.

A method which may be used for the preparation at home of a small number of tuberculin patches suitable for the patch test for tuberculosis is as follows.

Filter paper of the quality known as "Whatman Number 1" is cut into strips eight millimetres or one-third of an inch wide. The strips to a total length of about 30 centimetres, or one foot (which can be cut from a single seven-centimetre disk) are laid on a piece of metal gauze and are saturated (but only just saturated) with tuberculin, preferably the synthetic-medium old tuberculin as indicated above. This may be done with an eye pipette kept expressly for the purpose. The pipette may be marked on the side so that 0·5 cubic centimetre may be measured with it. It is found that strips of filter paper of the total length mentioned above, that is to say, of a total area of about 25 square centimetres, or 4·0 square inches, are just saturated by 0·5 cubic centimetre of tuberculin. The saturated strips are dried in a desiccator or in a warm, dry place out of direct sunlight, being turned over once or twice with forceps during the process. When they are dry they are again saturated with tuberculin and dried again. When they are again dry a spool of waterproof adhesive tape one inch wide and a yard long is unrolled, the strips are cut into squares and the squares are applied to the adhesive surface with the forceps at a distance of two-thirds of an inch from one another—that is to say, so that one square is applied for every inch of tape. The spool is then rewound and kept in a cool, dry place.

The Application and Reading of the Patch Test.

It will be observed that nearly all the results of the application of the tuberculin patch test which have been reported in the literature have concerned children, while accounts of its application to a large number of adults are lacking, so that it might be inferred that the test was not reliable in adults. This is indeed the case, and in the course of the application of the Mantoux test and the patch test to a large number of persons it was found that some 15% of adult reactors to the Mantoux test did not react to the patch test. No reason for this has been discovered; it does not appear to be related to the texture of the skin nor to its dryness or moistness. Nor does it appear to be related to the intensity of the reaction to the Mantoux test; some who reacted weakly to the Mantoux test reacted perceptibly (though never sharply) to the patch test, while some who reacted sharply to the Mantoux test did not react at all to the patch test.

The author considers that the best site for the application of the patch test is the soft skin of the medial aspect of the arm, half-way between the elbow and the axilla. It has been found that this is simpler than the application of the patch to the chest or back, as others have recommended; and further, a reaction produced on the back or chest of a child often seems to cause the parents great concern, while a reaction produced on the arm does not usually worry them. For women wearing short sleeves the patch should be concealed by the sleeve, if possible.

The skin is rubbed with a pledget of cotton-wool moistened with ether before the patch is applied. The patch, cut from the reel immediately before application, consists of an inch square of adhesive plaster with a smaller square of tuberculin-impregnated paper in its centre.

The patch is removed after forty-eight hours and the site of its application is inspected forty-eight hours after its removal. If the patch is removed after thirty-six hours and the site inspected twelve or fifteen hours later, in the majority of reactors the reaction is already apparent; but this technique is not to be recommended. A reaction consists of a miliary eruption where the paper

was in contact with the skin; there may be only two or three minute pimples, but these are readily recognizable after a little experience; or, on the other hand, the eruption may be confluent and consist of a red raised area. The reacting area may be slightly irritable, but it is not sore, though it may look sore. No by-effects or constitutional disturbances have been reported.

Sometimes in children and rarely in adults the skin is sensitive to the adhesive coating on the plaster; but any redness due to the plaster can easily be distinguished from a reaction to the test, because the area of skin in contact with the paper is protected from the plaster, and in the absence of a reaction to the test does not become erythematous.

Interpretation of Reactions.

In children up to the age of fifteen years, failure to react to the patch test is almost as good evidence of the absence of tuberculous infection as is failure to react to the Mantoux test. In adults, failure to react to the test should be interpreted with greater reserve; the Mantoux test is more suitable than the patch test for excluding a diagnosis of tuberculosis in adults. In children, a reaction to the patch test denotes that the child has had occasion to resist the tubercle bacillus, and a reaction to the test in a child should lead to an examination of the parents for tuberculosis.

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THE DIAGNOSIS OF INTRAVENTRICULAR HÆMORRHAGE.

By R. S. STEEL,
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RELATIVELY few medical men have an opportunity of observing from the beginning the signs of a cerebral vascular catastrophe. The onset is usually a sudden, severe headache. Such a headache developed in a patient of mine while I was talking at the bedside. The brief clinical history and physical findings in this case serve to outline the syndrome pointing to hæmorrhage into the ventricles of the brain.

Reports of Cases.

Mrs. G., aged seventy-two years, was a very active woman. She had had a boil on the left leg and had not felt in her usual health for three weeks. She complained of a boil on the anterior abdominal wall. There were no other symptoms. The time was 6 p.m., and suddenly, in my presence, she developed an intense headache in the parietal region. Two minutes later she vomited. She writhed about on the bed and requested no sedatives. The speech was slightly slurred. The restlessness persisted for nearly an hour; then she lapsed into unconsciousness.

On examination of the patient one hour after the onset of the headache unconsciousness was complete and the breathing was slightly increased in depth. The pupils were both pinpoint in size; there was slight but discernible rigidity of both arms and legs (approximately the same in upper and lower limbs), and bilateral Babinski reactions were obtained. Owing to the bilateral nature of the findings and the early rigidity, a diagnosis of intraventricular hæmorrhage was made. The patient died at the end of eleven hours. No post-mortem examination was performed.

The next patient I observed with a similar history and identical findings was admitted, under my care, to the Royal Prince Alfred Hospital about the same time.

Mr. S., aged forty-seven years, an office worker, apparently in his usual health, was suddenly seized with a headache and vomited while sitting at his desk at 3 p.m. He became unconscious and was conveyed to the hospital. I examined him at 4.30 p.m. He was unconscious, there were no voluntary movements of the limbs, and breathing was slightly increased in depth. The pupils were both contracted to a pin-point size. Slight rigidity of the limbs was noted on passive movement, somewhat more pronounced in the arms than in the legs, and bilateral Babinski reactions were obtained. The diagnosis of intraventricular hæmorrhage was made, and his relatives were informed that he would probably not live beyond 3 a.m. He died eleven hours after the onset of the headache.

Post-mortem examination revealed an aneurysm of the circle of Willis, which had ruptured, and the blood had ploughed its way through the brain tissue and ruptured into the left lateral ventricle, filling the third and fourth ventricles with blood.

Discussion.

A number of patients with similar signs have been observed, and the similarity of these cases led to the study of one hundred case records of cerebral hæmorrhage (non-traumatic) at the Royal Prince Alfred Hospital. The object was to determine the clinical value in an obvious case of cerebral hæmorrhage with early onset of unconsciousness, of the syndrome characterized by: (i) bilateral pin-point pupils, (ii) early bilateral rigidity, (iii) bilateral Babinski reactions.

Of the one hundred cases studied, a post-mortem examination was made in 37 (Table I).

TABLE I.

Total Number of Cases.	Patients Died.		Discharged from Hospital, Relieved or Unrelieved.
	Post-mortem Examination Held.	No Post-mortem Examination.	
100	37	37	26

In a few cases, two or more hæmorrhages were found isolated from one another. Further post-mortem studies showed that hæmorrhage on the left side of the brain was slightly more frequent than hæmorrhage on the right. A similar number of patients (37) who died were not subjected to post-mortem examination, and 26 patients were discharged from hospital relieved or unrelieved.

Of the 37 cases in which a post-mortem examination was made, intraventricular hæmorrhage was found in 27. The site of the origin of the hæmorrhage which found its way into the ventricles lay in any part of the brain—cerebral hemisphere, pons, cerebellum *et cetera*. In a few cases it was uncertain where the hæmorrhage began on account of the great destruction of brain tissue. No attention is given to the site of origin, or to the ploughed track of the hæmorrhage (except in the case of pontine hæmorrhage), and special attention has been concentrated upon the 27 cases in which intraventricular hæmorrhage was found.

Unfortunately, as will be observed, the record of physical findings is incomplete in many instances. They have been divided into four groups (see Table II). Group I, in which no physical findings are recorded before death, consisted of five cases. (The patients were either dead on admission to hospital, or died soon afterwards.) Group II consisted of three cases, in which the original site of the hæmorrhage was in the pons. These are considered apart from the others on account of the frequent finding of bilateral pin-point pupils in pontine hæmorrhage. Group III consisted

of 15 cases which suggest the syndrome of bilateral pin-point pupils, early bilateral rigidity and bilateral Babinski reactions. Group IV consisted of four cases; the record of pupillary and other signs excludes these cases from the previous group.

TABLE II.

Intraventricular Hæmorrhage. (Pons healthy.)

Case Number.	Bilateral Pin-Point Pupils.	Early Rigidity.	Bilateral Babinski Reaction.
I	No record.	+	+
II	+	+	+
III	+	+	No record.
IV	+	No record.	No record.
V	+	+	+
VI	+	No record.	No record.
VII	+	+	No record.
VIII	No record.	No record.	+
IX	+	+	No record.
X	No record.	No record.	+
XI	No record.	+	+
XII	+	+	+
XIII	+	+	+
XIV	+	+	+
XV	+	+	+

Pontine hæmorrhage, with the recorded physical findings, will be tabulated later.

Care has been taken in Group III to include no cases in which physical findings were contrary to the syndrome being described. Included in this series of 15 cases, however, will be noted "not recorded" in many cases (see Table II). Here, the physical finding has been omitted from the records by the examining doctor. The recorded physical findings in the light of the post-mortem report make them worthy of inclusion in this group. Only six of the 15 records give the complete syndrome. In the remaining nine cases, no record is made of one or of two of the three signs; yet, on the other hand, there is no record which can justify their inclusion in Group IV.

Table III shows the presence of the three signs marked "+" if recorded, and "no record" when missing from the history. From the clinical histories it is obvious that no attempt had been made to elicit the sign in a number of instances.

The four cases belonging to Group IV are set out in Table III. The recorded signs preclude them from being included in the previous table.

TABLE III.

Intraventricular Hæmorrhage not Showing the Syndrome.

Case Number.	Pupils.	Limbs.	Plantar Responses.
I	Dilated.	No record.	No record.
II	Dilated.	Rigid.	Flexor.
III	Dilated.	Flaccid.	Flexor.
IV	No record.	Flaccid.	Right, flexor; left, extensor.

The duration of some of these cases was many days. It is probable that with more careful histories and attention to the onset of late signs, some at least would have been found, from complete records, to belong to the previous group.

Pontine Hæmorrhages.

Owing to the finding of bilateral pin-point pupils occurring frequently in pontine hæmorrhages, special attention was given to this type of hæmorrhage, to find out whether early rigidity and bilateral Babinski reactions occurred also.

As stated in Table II (Group II), there were three hæmorrhages in the pons with intraventricular involvement. Only one other hæmorrhage in the pons (no intraventricular hæmorrhage) was found at the 37 post-mortem examinations performed in the 100 case histories studied.

Owing to the small number, a further 100 histories were examined for hæmorrhage in the pons. This study discovered another four hæmorrhages found to be present in the pons. These eight cases are set out in Table IV and include all cases in 200 records in which a post-mortem examination was carried out, and hæmorrhage was found to have affected the pons, either primarily or secondarily to a more distant hæmorrhage. The findings are given in respect to the signs under consideration.

It is observed that bilateral pin-point pupils were present in six of the eight cases of hæmorrhage in the region of the pons. Examination of the limbs for spasticity gave no uniform finding, and the plantar responses were variable.

The pontine hæmorrhages in Cases I, II and III (Table IV) could be rightly included in Group III (since they had ruptured into the ventricles), except that in Case I the limbs are stated to be flaccid. This observation is probably incorrect. If the limb was merely raised and allowed to fall, no record of the rigidity could be given, because the rigidity would probably not be appreciated. To detect the rigidity, full range of passive movement should be carried out. Only then will the rigidity of the limbs be appreciated in the early part of unconsciousness and during the course of the illness.

Comment.

Bilateral pin-point pupils are found in (i) uncomplicated pontine hæmorrhage and (ii) intraventricular hæmorrhage, in which the primary bleeding may be situated in any part of the brain.

Early bilateral rigidity and bilateral Babinski reactions are found when hæmorrhage occurs into the ventricles of the brain, and are not found in a simple pontine hæmorrhage.

Intraventricular hæmorrhage may be primary or secondary. The primary type is uncommon, and was found in only one brain on post-mortem examination. The secondary type is, however, common, and was found to be present in 26 of the 37 post-mortem examinations. Although the number of cases examined is admittedly small, the frequency of secondary intraventricular hæmorrhage as reported here is probably not generally recognized.

Text-books on medicine give very little help in the clinical diagnosis of hæmorrhage into the ventricles of the brain. I have not been struck with the sign of head retraction mentioned by Beaumont and also by Conybeare, unless there is associated subarachnoid hæmorrhage. Some rigidity of the neck muscles may be present on flexion of the head, but it does not amount to head retraction. Nor have I been impressed by the "intense rigidity" of the limbs described by Conybeare, or by the tonic or clonic spasms of the limbs described by both authors. In my experience the rigidity to passive moment is definite, but

TABLE IV.

Pontine Hæmorrhage.

Case Number.	Primary or Secondary Hæmorrhage.	Intraventricular Hæmorrhage.	Pupils.	Limbs.	Plantar Responses.
I	Primary.	Yes.	Bilateral pin-point.	Flaccid.	No record.
II	Primary.	Yes.	Bilateral pin-point.	No record.	No record.
III	Primary.	Yes.	Bilateral pin-point.	Legs spastic.	Bilateral Babinski reaction.
IV	Primary.	No.	Bilateral pin-point.	Flaccidity.	Right flexor, left extensor.
V	Primary.	No.	Bilateral pin-point.	Flaccid except right arm.	Both flexor.
VI	Secondary.	No.	Both dilated.	Left side flaccid, right normal.	No record.
VII	Primary.	No.	Right dilated, left pin-point.	Right side flaccid, left side spastic.	Right flexor, left extensor.
VIII	Secondary.	No.	Bilateral pin-point.	Normal.	Both flexor.

not intense, is bilateral (sometimes it is more pronounced in the arms), and is found to be present at an early stage. The limbs are usually extended, and remain in that position from the onset of unconsciousness.

With reference to the bilateral Babinski reactions, Russell Brain has described signs of bilateral pyramidal lesions as an aid to diagnosis in these cases, and these findings point to their presence.

The medical attendant usually sees the unconscious patient, and in an obvious case of cerebral hæmorrhage, in which there is a rapid onset of coma with (i) bilateral pin-point pupils, (ii) early rigidity of the limbs coming on with the onset of coma and (iii) bilateral Babinski reactions, a diagnosis of intraventricular hæmorrhage can be made.

These signs are found particularly in those cases in which the hæmorrhage ruptures into the ventricles without delay. In these cases, too, death frequently follows about twelve hours from the onset of the symptoms.

In those cases in which there is a delay between the time of the original hæmorrhage and the time when the blood ruptures into the ventricles, characteristic signs will be found of the lesions in its early stage—for example, a hemiplegia. The delay may be a matter of some days. But in these cases the occurrence of pin-point pupils or bilateral extensor plantar responses at a later stage are signs pointing to intraventricular hæmorrhage as a secondary manifestation. These signs have been observed and recorded in a few of the histories studied. In these cases the expected rigidity of the limbs may be masked by the previous signs of hemiplegia. One could not expect to find bilateral pin-point pupils occurring in all the "delayed" cases, on account of the anatomical destruction to the brain tissue by the track taken by the blood on its way to the ventricles. In a case of hemiplegia in which there is a deepening of unconsciousness or some such manifestation of change in the condition of the patient, the appearance of an extensor plantar response on the unparalysed side, especially with some rigidity, is indicative of secondary intraventricular hæmorrhage. Further, it has been observed in these cases that the previously unaffected pupil may become constricted—all signs of an early and fatal termination.

Summary.

An attempt has been made to clarify signs pointing to a clinical diagnosis of intraventricular hæmorrhage.

A syndrome has been outlined consisting of (i) bilateral pin-point pupils, (ii) early bilateral rigidity, (iii) bilateral Babinski reactions.

This syndrome is found when a hæmorrhage ruptures into the ventricles of the brain without delay. It is associated with early and complete unconsciousness, and usually ends fatally in about twelve hours. The recognition of these signs, in whole or in part, in a case of cerebral hæmorrhage of some days' duration, serves to localize the track of the hæmorrhage, and to foretell the hour of death.

Twenty-seven post-mortem examinations at which intraventricular hæmorrhage was found are analysed.

The signs of eight pontine hæmorrhages (three with and five without intraventricular hæmorrhage) are discussed and the simple pontine type is distinguished from intraventricular hæmorrhage.

Reports of Cases.

PREGNANCY COMPLICATED BY A DOUBLE UTERUS: A REPORT OF TWO CASES.

By G. SHEDDEN ADAM, F.R.C.S.E., M.R.C.O.G.,
Brisbane.

RELATIVELY few of the wide variety of congenital malformations affecting the female generative organs are of clinical importance unless complicated by pregnancy. Embryologically the uterus and vagina are formed by the fusion of the two Müllerian ducts, the union taking place from below upwards. Lack of complete fusion with disappearance of the intervening septum, at any point, or throughout the length of the two canals, explains most of the abnormalities observed, and the rudimentary development of one duct will account for the remainder.

Probably the most serious complication of these malformations is the occurrence of pregnancy in a rudimentary uterine horn, because rupture of the gestation sac in these cases about mid-term is almost inevitable if the condition is undiagnosed, and is associated with the most profuse hæmorrhage. Kehner gives the mortality rate from this accident as 82%.

It is for this reason that demonstrable malformations of the lower part of the genital tract, such as a septate vagina, should, if pregnancy supervenes, lead the clinician to suspect further abnormalities and to make a careful bimanual examination of the pregnant uterus.

In cases of double uterus complicated by pregnancy, whether associated with a single cervix (*uterus duplex unicornis*), as in the instances to be quoted, or with a double cervix (*uterus duplex bicornis*), the pregnancy may be entirely uneventful; but, on the other hand, a variety of complications may ensue. As an example De Lee quotes the following possibility: the decidua on the empty side may be cast out whilst the pregnancy continues on the opposite side. Clinically the condition would resemble an incomplete abortion, and the subsequent curettage may destroy the intact ovum. Usually, however, the decidua from the empty side comes away with the lochia during the puerperium. Abortion, of course, may involve the pregnant half (as in Case II), and it may be difficult to curette the uterus, especially if there is a vaginal septum and only one cervix is present. Müller records cases of menstruation from the empty horn during pregnancy.

Labour may be normal; but weak contractions and post-partum atony have been observed. The non-pregnant portion of the uterus may prolapse under the other and act like a tumour incarcerated in the pelvis (as in Case I). Septate uteri may predispose to an oblique or transverse lie of the fœtus; in one case quoted by De Lee the infant presented by the breech, straddling the partial septum.

The placenta may be adherent to the septum and thus be a cause of post-partum hæmorrhage. The normal polarity of the uterus may be upset, with resulting incoordinate contractions and slow dilatation of the cervix, although this certainly did not obtain in Case II.

It would seem that the most satisfactory alternatives in the management of these cases are the surgical removal of the non-pregnant portion of the uterus during the first half of pregnancy if it seems likely that abortion may otherwise occur from the increased intrapelvic pressure; or, in the absence of such evidence, to allow the pregnancy to continue to term, assess the probability that the non-pregnant half will cause an obstruction, and then decide whether a Cæsarean section will be needed. The removal of the non-pregnant side, if considered necessary, may be combined with the Cæsarean section; but for technical reasons its earlier or subsequent removal would probably be preferable.

Case I.

Mrs. D.H., aged twenty-seven years, was pregnant for the second time. In 1936 she had been delivered, after considerable difficulty, of an infant weighing nine pounds, which was stillborn. There had apparently been a brisk hæmorrhage following the confinement. The puerperium, however, had been uneventful and there had been no further pregnancies until the present one. When the patient was first seen examination revealed the free hypertrophied fringes of what apparently was a torn vaginal septum, which had originally extended up the whole length of the vaginal canal in the sagittal plane. The hypertrophied fringe of the lower end of the posterior half of the torn septum was protruding through the vulval orifice. A large, tender, soft, non-cystic mass filled the pouch of Douglas; it could not be displaced from it. The cervix was single, lacerated and displaced forwards. The infant was presenting by the breech and the legs were extended.

In view of the developmental abnormality present in the lower part of the genital tract, it was considered probable that other abnormalities might also be present and that the mass in the pouch of Douglas was possibly the non-pregnant half of a double uterus. The obstetric history, moreover, gave a clue to the likelihood of trouble arising from this complication, and in view of the loss of the patient's first infant it was decided that delivery should be effected by Cæsarean section. This was carried out on July 12, 1941, and a number of interesting observations were made. A double uterus was present; the non-pregnant half, to which were attached the right Fallopian tube and round ligament, had become displaced behind the pregnant

half. The latter, to which were attached the left Fallopian tube and round ligament, had undergone some degree of axial rotation in its long axis, so that the adnexæ presented immediately to the left of the abdominal incision. The extent of non-union of the Müllerian ducts was indicated by the fact that the site of attachment of the non-pregnant to the pregnant half was approximately at the level of the internal os. A classical Cæsarean section was performed after correction of the rotation. The infant was alive and well and the puerperium was uneventful.

Case II.

Mrs. H.C., aged twenty-five years, was pregnant for the second time; her first pregnancy had terminated in a miscarriage in January, 1940, after three and a half months' gestation. She first reported on this occasion in January, 1941, when three months pregnant, complaining of dragging pain in both iliac fossæ, worse on the left side. Pelvic examination revealed the uterus to be much displaced to the right, and a soft, non-cystic, tender mass could be felt on bimanual examination, filling the pelvis on the left side.

In view of the patient's previous miscarriage and its probable relationship to the intrapelvic mass, she was advised to enter hospital for observation, with the possibility that surgical intervention might be necessary. However, six weeks passed before she would agree to this; but early in March, 1941, when five months pregnant, she entered hospital. The displacement of the uterus to the right was now even more pronounced, the cervix pointing downwards and to the left. The mass on the left side could now be defined by palpation through the abdominal wall on that side, and it had become tender.

Abdominal section was performed on March 11, 1941, and disclosed the presence of a double uterus, the right half of which was enlarged to the size of a five and a half months' pregnancy. The left non-pregnant portion was soft and enlarged to the size of an eight weeks' pregnancy. It occupied the left half of the pelvis and joined the pregnant portion at the level of the internal os. The right and left adnexæ were attached to the pregnant and non-pregnant halves respectively. The latter was removed without difficulty, there being only one cervix, which was left practically intact. Examination of the endometrial lining of the portion removed showed a thick decidual reaction. The convalescence was unattended by any signs that the pregnancy had been disturbed, and the patient left hospital on March 30, 1941. She continued to attend the ante-natal clinic; external cephalic version was carried out on May 16, and labour commenced on July 5. The cervix dilated without difficulty, the duration of labour was relatively short, and the delivery was unassisted.

Acknowledgements.

My acknowledgements are due to Dr. H. McLelland, Dr. L. W. Gall and Dr. R. B. Charlton, of the part-time staff of the Brisbane and South Coast Hospitals Board, for their consent to the publication of these cases.

ABSENCE OF THE VAGINA SUCCESSFULLY TREATED WITHOUT OPERATION.

By KATE CAMPBELL,
Melbourne.

Clinical Record.

THE patient was first seen at the age of sixteen years because of non-appearance of the menses. She had always been a healthy girl. On examination the secondary sexual characteristics were well developed. The external genitalia appeared normal, except that the *ostium vaginæ* was imperforate. It was assumed that an imperforate hymen was present. However, later, a further examination was made under general anæsthesia, and it was then found that the vagina was completely absent, the apparently imperforate hymen being the continuation of the vulval mucous membrane. *Per rectum* a small rudimentary knob was felt in the position of the uterus.

When the patient was aged twenty-six years, treatment was begun on the lines described by Eugene Steinmetz, based on the method of Robert T. Frank. Briefly, Steinmetz suggests the use of "Pyrex" glass tubes of increasing length and diameter, as follows: first tube, five-sixteenths of an inch by three inches; second tube, five-eighths of an inch by three inches; third tube, three-quarters of an inch by three and a half inches. The patient is instructed to insert the first tube in the direction of the vagina and to keep it *in situ* for half an hour three times a day for one week. It is stated that it penetrates almost to full length in two to four weeks. The tube is then shortened to two and a half inches and the patient retains it overnight by means of a pad and a T binder. Six to eight weeks should be sufficient time. The same procedure is then adopted with the second tube, and after a few weeks with the third tube. Steinmetz states that normal coitus should then be satisfactory, that the vagina should admit two fingers with a penetration of two and a half inches, and that the canal should be lined with soft resilient mucous membrane.

In this case all these claims were substantiated, and as the condition is a rare one, details of the progress may be of interest. The dilators were made of vulcanite to the specified dimensions by Messrs. Felton, Grimwade, of Melbourne. Two weeks after the first vaginal dilator had been used three times a day, it was found to penetrate to a depth of two inches. Four weeks from the beginning of treatment it penetrated its full length after five minutes. There was obviously some muscle spasm, which could be felt by the patient to yield. There was some ulceration of the posterior vaginal wall at this stage. It was thought that the use of œstrin pessaries might make the mucous membrane more pliable, and these were ordered at night. The patient considered that these helped her considerably. At this stage the dilator was shortened to two and a half inches and was retained all night. Five weeks from the commencement of treatment she was given the second dilator to insert three times a day, and was instructed still to retain the first size at night. After six and a half weeks the second dilator penetrated two inches, and at a vaginal examination two fingers penetrated two and a half inches. After nine and a half weeks she was able to retain the second dilator for some hours, but the vagina became painful and bled slightly. At a vaginal examination two fingers still penetrated two and a half inches. After eleven and a half weeks the third dilator penetrated to two inches, and at a vaginal examination two fingers penetrated to a depth of two and seven-eighth inches.

A spasm of muscular tissue about one inch up the vagina was evident, but this quickly relaxed. The patient was instructed to use the dilators three times a day. After twelve and a half weeks the patient was married. She reported that coitus was normal and satisfactory to both partners. When the patient was examined five months later the vagina admitted two fingers to a depth of two and a quarter inches and was broader than before. It had the appearance of an ordinary vagina.

Discussion.

Some practical points which cropped up during treatment may be of interest. (i) Help was derived from œstrin pessaries. (ii) The patient found that a dilator intermediate in size between the first and second was desirable, and one was made measuring half an inch by two and a half inches; this she found helpful. (iii) When the patient used a larger sized dilator during the day she kept the preceding size *in situ* at night. (iv) The most interesting feature was the rapidity with which this artificial vagina could be formed. The ease of treatment and freedom from risk as compared with surgical treatment need no comment.

Bibliography.

E. R. Steinmetz: "Formation of Artificial Vagina", *The Western Journal of Surgery, Obstetrics and Gynecology*, Volume XLVIII, March, 1940, page 169.

Reviews.

EXPERIMENTAL PHYSIOLOGY.

"EXPERIMENTAL Physiology for Medical Students", by Professor Harris, of London Hospital Medical College, is a book of 292 pages setting out a series of experiments, most of which can be done by the student, others to be shown as demonstrations.[1] The descriptions of the experiments are clear and from their performance the student would derive a very extensive factual knowledge of the subject of physiology. There are two outstanding defects in the book: the first is that the author does not indicate to the student the general principles of the experimental approach to biology, and the second is that the experiments are set out in a form which is so explicit and the results to be expected are so well described that they become exercises rather than experiments. Otherwise the book can be recommended to any school which has the apparatus required in the book.

[1] "Experimental Physiology for Medical Students", by D. T. Harris, M.D., D.Sc., F.Inst.P.; Third Edition; 1941. London: J. and A. Churchill Limited. Medium 8vo, pp. 303, with 248 illustrations and plate in colour. Price: 15s. net.

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CONGENITAL CATARACT FOLLOWING GERMAN MEASLES IN THE MOTHER.

At the third annual meeting of the Australian Ophthalmological Society (British Medical Association), held at Melbourne in October, 1941, Dr. N. M. Gregg, of Sydney, reported an interesting series of cases in which congenital cataract occurred in babies whose mothers had suffered during the early stages of pregnancy from a condition that was diagnosed as German measles. The series is so striking and the sight of the children is so seriously affected that the facts must be made known without undue delay to the general body of the medical profession. Dr. Gregg's paper will be published in due course in the *Transactions of the Ophthalmological Society of Australia*; we are indebted to Dr. Gregg and to the council of the society for permission to make reference to it in these columns prior to its publication.

Early in 1941 Dr. Gregg, who is honorary ophthalmic surgeon to the Royal Alexandra Hospital for Children, Sydney, noted among the babies brought to that institution for treatment a number who were suffering from cataract. The babies were of small size and ill nourished; they were generally difficult to feed, and as a matter of fact were often on this account taken to the pædiatrician before they were considered well enough to be placed under the care of the honorary ophthalmic surgeon. The cataracts were generally, but not always, bilateral and had almost invariably been present since birth as dense white opacities completely occupying the pupillary area. With the instinct of a true clinician, Dr. Gregg set to work to discover the cause of the condition. He could find nothing to explain it, but was struck by the fact that in every instance the mother, either during the early days of her pregnancy or just before it, had suffered from an illness which was diagnosed as German measles. Obviously, inquiries had to be extended further, and Dr. Gregg then wrote to ophthalmologists in Sydney and in centres in other States telling them of his observations and asking whether they had come across similar cases. As a result of this inquiry 78 cases of this unusual sequence of events have been discovered; 13 were in Dr. Gregg's own series. In his Melbourne paper Dr. Gregg described the condition of the patients in some detail. Full mydriasis was difficult to obtain; an unusual number of the patients were intolerant of atropine, and it was necessary to rely on repeated instillations of homatropine. When the pupil was dilated the opacities appeared densely white, sometimes quite pearly, in the central area; but between this area and the periphery of the lens was a zone with a less smoky appearance; outside the latter zone there was only a narrow ring through which a red reflex could be obtained. Since only the outermost layers of the lens were involved, it was thought that the pathological change must have begun in the early life of the embryo. Although the cataracts conformed generally to the description just given, Dr. Gregg divided the cataracts into two groups. In one the contrast between the larger and central dense white area and the smaller and more peripherally situated smoky zone was very pronounced. In the other the density of the cataract was more uniform throughout and might be described as an intermediate stage between the two layers of the other type. Incidentally it may be remarked that operation was easier to perform in one group than in the other; but that does not particularly concern us in the present discussion. What is important is that the appearance of the cataract did not, in Dr. Gregg's opinion, correspond to any of the morphological types of congenital and developmental lenticular opacities which have been described. He contents himself with describing it as subtotal. A point which adds to the difficulty of finding an explanation for the condition is the fact that in 16 of the 78 cases in the series the cataract was unilateral. Moreover, in 11 of the 16 monocular cases the affected eye was noted as being smaller than the other. For example, in one case autopsy revealed that the antero-posterior diameter was 1·6 centimetres and the transverse diameter 1·5 centimetres; in the unaffected eye the measurements were respectively 1·8 and 1·9 centimetres. The remaining important lesion reported in this series is a lesion of the heart. It is described as a congenital defect of the heart. The following description has been given by Dr. Margaret Harper of the findings in eight cases seen by her:

> All these babies were seen because of difficulty in feeding and failure to thrive. They all had symptoms suggesting a cardiac defect such as difficulty in taking the breast, they had to be fed in their cots by bottle and some by gavage. They were all in the acyanotic or potentially cyanotic groups of cardiac defects. None was cyanotic. There was a harsh systolic murmur over the base of the heart and down the sternum in all. Some had a thrill. All had signs suggesting the continuance of a fœtal condition or of a malformation of the heart.

In Dr. Gregg's series this condition was present in all but one case. In the whole series it was present in 46 cases; in 12 cases no record of the cardiac condition was made; in 12 cases it was recorded as "normal or apparently normal". In four cases in which a report was made about the condition the babies died and death was

sudden; in another the baby was ill nourished, and in three cases the report was "no defect noted". In three cases in which autopsy was performed a patent *ductus arteriosus* was found.

The medical man or woman who hears of these remarkable observations for the first time will be tempted to accept the German measles-cataract sequence without question as an example of cause and effect. But caution is needed. Dr. Gregg quotes opinions from the literature. Bereus expressed the view that congenital cataract may be due to a maldevelopment, a physical or chemical element acting on the developing lens, or inflammation during the embryonic or fœtal period. Duke Elder holds that "the ætiology of these opacities depends upon some disturbance of the development of the lens, but what the actual disturbance may be, or the precise mode of its action, is a matter of considerable doubt in most cases. Duke Elder thinks that toxic influences may also play a part in the production of opacities, and in his opinion it is conceivable that toxic or infective processes in the mother may cause a derangement in the lens of the fœtus or that causes such as an error of feeding or acute exanthemata in the infant may have a similar effect. Jaemsch concluded from his anatomical studies that an intrauterine inflammation was a frequent cause of total opacity of the lens. Dr. Gregg is inclined to the view that one condition causes the other. His view is expressed in the following words, taken from his paper: "If we allow the possibility of the lens being affected by infective processes in the mother, and if we find the same infection occurring at approximately the same period early in the pregnancy in almost all the cases, and if we then find that the babies of these mothers have cataracts of a more or less uniform type which involve the fibres formed at that period, then I think it is reasonable to assume that it cannot be a mere coincidence, but that there must be some definite connexion between that infection and the morbid condition of the lens." Dr. Gregg thus does not commit himself entirely to the cause and effect view of this sequence. The President of the Ophthalmological Society who presided over the session at which Dr. Gregg presented his paper, urged those present not to be too hasty in their acceptance of the cause and effect view. It is possible that the association between the two conditions is entirely fortuitous. This would be almost as difficult to prove as the cause and effect association. To begin with, though, as far as we can judge from Dr. Gregg's paper, the cataracts were all of the same unusual type, a history of measles in the mother was not present in every instance. In 68 of the 78 cases the history of German measles infection was definite. In two of the ten remaining cases the report "was negative for measles"; in one there was a history of kidney trouble; in two the report stated "history not asked for"; in the remaining cases the report was "no history of measles" or "not known". In some of these ten cases, then, measles might have occurred. Of course it must be granted that the signs produced by an infection of German measles may be so slight as to pass unnoticed by the patient and yet sufficiently severe to produce a lesion in susceptible tissue. It would perhaps be helpful if we could discover how many women suffered from German measles either immediately before or in the early stages of pregnancy and yet produced infants free from lenticular lesion; but such information is never likely to be available. The occurrence of a severe cardiac lesion in these children is most interesting, and the same must be said of the finding of microphthalmus. Dr. Gregg suggests that the congenital defect of the heart may be due to some toxic or infective process which brings about an arrest of development. It would be reasonable to expect that a toxic process capable of causing an arrest of cardiac development would leave other evidence of its presence in the heart or in other parts of the body of the fœtus. This has not so far been determined, though it is true that Dr. Gregg gave some details of one post-mortem examination in which hæmorrhagic spots were detected on the inner side of the pericardium and on the surface of the myocardium; the visceral pericardium over the upper anterior aspect of the left ventricle bore a "milk spot". It is not inconceivable that a toxæmia in the mother might in certain circumstances produce arrest of development in the fœtus. This would account for the cardiac but not for the lenticular condition of these patients. (There is no suggestion from Dr. Gregg that it would.) Inasmuch as the embryonic lens is transparent, congenital opacities in this tissue must always be aberrations of growth. They cannot be explained as representing the persistence of any structures, and are not a phase of any normal stage of development.[1] This brings us to the question of the German measles. The epidemic of German measles that occurred in 1940 in Australia was unusually severe and was followed by many complications. At the same time the infection known variously as Ingleburn throat, Puckapunyal throat and Woodside throat was rampant. (These infections were discussed by several authors in THE MEDICAL JOURNAL OF AUSTRALIA of January 4, 1941.) Dr. Gregg makes the entirely reasonable suggestion that some of the rashes diagnosed as due to German measles were occasioned by a toxic erythema from one of these other severe infections. Many persons will at once ask themselves whether the use of sulphanilamide in the treatment of infected mothers may not have had a bearing on the formation of cataract in the fœtus; but Dr. Gregg, in a personal communication, has stated that in no case in the series of 78 cases reviewed by him was a sulphanilamide compound exhibited.

The facts of the observations made by Dr. Gregg and his colleagues have been set out. The problem, it will be agreed, is not entirely an ophthalmic problem; it is one which concerns general medicine to a very large extent. To say that the causal relationship between German measles or similar infection and the congenital cataract in these babies is not entirely proven does not detract in any way from the astuteness of Dr. Gregg's observations; nor does it belittle the keenness of his quest. This is the kind of problem that must be pursued until the full light of understanding has been shed upon it. Though we sometimes have to do so temporarily, we must not take permanent refuge behind what Duke Elder has called those meaningless terms so frequently used in pathology—malnutrition, degeneration and toxic action.

[1] I. C. Mann, *Transactions of the Ophthalmological Society of the United Kingdom*, Volume XLV, 1925, page 696, quoted by S. Duke Elder in "Recent Advances in Ophthalmology", 1934, page 330.

Current Comment.

CONSENSUAL REACTION OF THE SKIN TO TEMPERATURE CHANGES.

LEWIS showed that if an area of the skin is warmed the vaso-dilator response is not confined to the region stimulated and he postulated the formation locally of a histamine-like body or, simply expressed, an H-substance capable of diffusion. Similarly the application of cold will produce vaso-constriction beyond the confines of the chilled surface. Much ingenuity was once displayed in British medical writings to explain why wetting of the feet should so often be followed by a cold in the head or a sore throat; we now know that lowered resistance through vaso-constriction of head and neck can be an adequate or at least a contributory cause.

The quantitative measurement of the consensual vascular response has recently been carried out by a very elegant method by two Swedish investigators, O. Hultén and Stig Källmark.[1] The opposite hand to that stimulated is immersed in a known volume of water contained in a "Thermos" flask which acts therefore as a calorimeter. The initial temperature of the water is set at 20° C. and the rise in temperature, measured in units of 0·1° C., is plotted against the time. The curve obtained empirically in this fashion has been found to be exponential, and so if the logarithms of the temperatures are taken, a straight line is obtained. The angle which this straight line makes with the x axis is a measure of the heating capacity of the immersed hand. Various experimental procedures were adopted such as impeding the circulation by the inflated cuff of a blood-pressure apparatus. That the consensual dilatation is not due to a general rise of blood temperature had already been demonstrated and this was confirmed by taking thermometric readings from the rectum. The chief conclusions of this research are that the consensual reaction to warming the skin is due to a chemical agent which gains admission to the general blood stream, whereas the response to cold is purely nervous, the vaso-constriction being wholly due to reflex sympathetic activity. Another Swedish investigator, Runar Brenning, has endeavoured to ascertain the nature of the hormone responsible for the response to warmth.[2] If the skin is heated to a degree that causes pain, then undobtedly an H-substance is liberated from the excited tissue; but if the warmth is moderate and below the protopathic threshold, consensual vaso-dilatation can still occur. In these cases pulse rate, electrocardiogram, arterial pressure and gastric secretion showed no indication that a vagal hormone was at work. Whatever be the chemical agent responsible, it is not, according to Brenning, of a histamine character.

[1] *Upsala Läkareförenings Förhandlingar*, New Series, Volume XLV, May, 1941, page 143.

[2] *Ibidem*, page 157.

THE BOMB-PROOF CIVILIAN.

EVER since illustrated journals, newsreels and newspaper photographs have begun to arrive in Australia, portraying the extent and savagery of air raids on prominent English cities, many Australians have spoken and thought of the equal devastation which may be expected in the psyche of the inhabitants. Newspapers and the speeches of statesmen are expected to omit reference to such a topic, or even to protest too much that the civilian morale was never higher *et cetera*. The truth is better given in personal letters from the civilian front line or in the cold statistics of psychiatry clinics. Arthur Harris is a medical officer of such a unit established in close proximity to a large refugee reception unit and to one of the most heavily bombed quarters of London, with a population of 700,000. He has undertaken a review of admissions to his clinic covering the period during which Belgium and Holland were invaded, and the battle for Britain in September, 1940.[1] Administrative changes do not permit of any numerical conclusions as to percentage incidence of post-bombing neurosis among his neighbours, but the total psychiatric damage has been remarkably small. In nearly every instance in which recovery has been delayed there is a history of psychopathy or anxiety. Harris makes the first observation that although modern aerial warfare may precipitate a mental crisis in the predisposed, there are very many instances in which war service solves individual difficulties, such as those caused by unemployment, a failing business, domestic unhappiness *et cetera*, so that the net balance is not so huge as superficial consideration may anticipate. Several authors have observed that war time brings an improvement in chronic depressives and hypochondriacs which they ascribe to the increased opportunities for work and companionship. This is parallel to the views expressed in a recent address by Professor W. S. Dawson upon the prophylactic value of work in war-time charities, national emergency service organizations *et cetera* for restless and anxious civilians. The anxiety of many a mother is mitigated by the opportunity of sharing her cares with other relatives at a knitting circle.

Harris was surprised at the absence of cases of conversion hysteria and of organic confusional states following exposure to blast, carbon monoxide or anoxæmia. There is a tendency among relatives and also perhaps among medical practitioners to ascribe all neuroses and psychoses at present to the chronic or acute stresses of warfare, forgetful of the fact that the same stresses that helped to fill psychiatric clinics in peace time are still operative. Thus the investigation of a skilled social worker into the family and economic background and the solicitation of an adequate personal history by the medical observer are as important as ever if a correct diagnosis and prognosis are to be formulated. Thus Harris found that the syndromes encountered did not differ materially from those met with in peace time. These were senile dementia, depression mania, schizophrenia, psychopathic personality and psychoneurosis, in this order of frequency. Naturally the general stress of the war situation was considerable and was occasionally the chief factor; but frequently an experience of bombing merely determined the onset of a breakdown to which constitutional and environmental factors had been conducive. He quotes two individuals in whom the acute mental trauma of an air attack and its consequences had precipitated the mental component of organic nervous disease, in one a glioma of the temporal lobe, and in another general paralysis. A large group was composed of patients who were previously "borderline institutional cases" and in whom the precipitate change of environment, the general apprehension and disturbance, had precipitated mental relapse. Senile dements were by far the commonest of this class, but congenital defectives and chronic schizophrenics, whom their families had hitherto been able to look after satisfactorily, were also seen. Old people living by themselves, who were unable to cope with the blackout regulations, became confused, hostile and aggressive, often refusing to seek the safety of the shelters and insisting on staying in the house alone.

Harris concludes that only 23 of 435 admissions to his institution were directly attributable to air raids. Of these, 13 followed acute psychic trauma, nine prolonged mental stress, and one cerebral contusion. The commonest reactions were depression and anxiety. The astoundingly few mental casualties, if this is a reflection of the consequences of aerial bombardment throughout the United Kingdom, must be a depressing revelation to the enemy and increase his anxiety as to the outcome of it all.

[1] *The Lancet*, August 9, 1941.

Abstracts from Medical Literature.

THERAPEUTICS.

Peptic Ulcer.

M. J. SCHIFFRIN AND S. A. KOMAROV (*American Journal of Digestive Diseases and Nutrition*, June, 1941) discuss the inactivation of pepsin by compounds of aluminium and magnesium. Colloidal aluminium hydroxide inactivates pepsin. In this study aluminium phosphate and chloride and magnesium trisilicate were mixed in varying proportions with gastric juice and a 1% solution of pepsin in 0·1/N hydrochloric acid solution. The mixtures were allowed to stand and then investigated for active pepsin content. Aluminium hydroxide, phosphate and chloride were tested, and all exhibited a strong inhibitory effect on peptic activity, while magnesium trisilicate produced hardly any inhibitory effect. Aluminium hydroxide and phosphate buffer the acid, precipitate pepsin at low acidity and inhibit peptic digestion even in the presence of high acidity, such as occurs in the stomach during digestion. A combination of properties, such as those possessed by the aluminium compounds, seems to be highly desirable in any agent to be used in the treatment of peptic ulcer.

Histaminase.

H. NECHELES, W. H. OLSON AND W. SCRUGGS (*American Journal of Digestive Diseases and Nutrition*, June, 1941) describe an experimental study on histaminase. This substance has been recommended for the treatment of all disturbances in which histamine plays a role. Bubkin suggested that histamine might be a factor in the gastric secretion of hydrochloric acid and possibly in the genesis of gastric ulcer, and histaminase has been reported as beneficial in peptic ulcer. The authors were doubtful of the clinical application of histaminase because there is no good evidence that any enzyme was absorbed through the gastro-intestinal tract, because histaminase is destroyed by pepsin as well as trypsin, and because histaminase is present in the small intestine and kidneys in such amounts that a few units of injected histaminase can make little difference. All available preparations of histaminase were used in an experimental study, by intravenous, subcutaneous, intramuscular and intraduodenal routes. It was found that histaminase had no depressant action on salivary, biliary, gastric or pancreatic secretion of dogs stimulated by histamine; nor had it any depressant effect on gastric secretion of dogs following a meat meal. It had no effect on gastric motility of dogs stimulated by insulin or prostigmine. Preparations of torantil were variable in effect.

Mercurial Diuretics and Heart Failure.

WILLIAM EVANS AND THOMAS PAXON (*The British Heart Journal*, April, 1941) report the results of a clinical trial of certain mercurial diuretics in the treatment of 50 patients suffering from heart failure, and draw a comparison of their relative diuretic potency. Thirty of the patients were men and 20 were women. Hypertension was the cause of the failure in 28, mitral stenosis in 12, and other less common conditions in 10 instances. The need for mercurial diuretics was determined by finding evidence of fluid retention on clinical examination; but in some cases of hypertensive heart failure frank œdema could not be demonstrated, and in these the symptom of breathlessness and the X-ray appearance of pulmonary congestion gave proof of suitability for this form of therapy. Each patient was admitted to hospital and confined to bed during the investigation, the fluid intake was recorded daily and restricted to 35 ounces, and the daily output was also recorded. The authors refer to the "diuretic index", which is the excess of the daily output of urine over the fluid intake. "Esidrone", "Mersalyl", "Neptal", "Novurit" and "Salyrgan" were submitted to trial and were administered intravenously or intramuscularly in doses of two cubic centimetres, by mouth, and by rectal suppository in the case of two preparations. The best method of administration of these drugs, as well as the best means of augmenting their natural diuretic action was investigated. The authors found that "Neptal" and "Esidrone" administered intravenously or intramuscularly produced the largest diuresis, rather larger than "Salyrgan", and much larger than "Mersalyl". The intravenous method almost always induced greater diuresis (average diuretic index of 76) than the intramuscular method (average diuretic index of 56). "Novurit" gave better results as a suppository than "Salyrgan". "Neptal" tablets by mouth were more efficient (average diuretic index of 32) than "Mersalyl" tablets (average diuretic index of 19), "Salyrgan" tablets, or "Novurit" suppositories given rectally (each with a diuretic index of 17). The authors tried eleven different forms of premedication used prior to the administration of the mercurial diuretic, and found thirty grains (two grammes) of ammonium chloride given two hours before the mercurial drug to be the best form of premedication. Enteric chocolate-coated tablets, each containing 7·5 grains, proved the most convenient form of dispensing ammonium chloride. The authors conclude that for a patient confined to bed with heart failure, and especially with œdema, standard treatment should include the injection of a mercurial diuretic (two cubic centimetres) intravenously or intramuscularly every third day, preceded by the administration of 30 grains of ammonium chloride by mouth two hours before, on each occasion, and that during the ambulatory stage the patient should take "Neptal" tablets (three in all or 0·48 gramme) twice a week in the more severe cases and once a week in the less severe, after the same premedication, and receive an intravenous or intramuscular injection (two cubic centimetres) at intervals according to need.

Digitalis and Acceleration of the Heart in Auricular Fibrillation.

WALTER MODELL, HARRY GOLD AND HAROLD H. ROTHENDLER (*The Journal of the American Medical Association*, May 17, 1941) discuss the use of digitalis to prevent exaggerated acceleration of the heart during physical exercise in patients with auricular fibrillation, and base their conclusions upon the results of experiments upon eleven ambulatory patients with auricular fibrillation showing varying degrees of heart failure. They state that the average patient with auricular fibrillation has acceleration of the ventricular rate during exercise chiefly, if not entirely, by decrease of the vagal tone, and in these cases blocking of the vagus by means of an intravenous injection of two milligrammes of atropine sulphate accelerates the ventricles to the same maximum level as extreme physical exertion. In some patients, however, especially those with advanced heart failure, an accessory mechanism for acceleration may also be invoked during extreme physical effort. The authors found that exaggerated acceleration of the ventricles caused by physical exercise in patients with auricular fibrillation can be prevented in most cases by "extravagal" digitalization, a state in which the ventricles are slowed chiefly by the direct action of digitalis on auriculo-ventricular conduction and in which vagal tone is for the most part lost. This is produced by relatively large doses of digitalis, and in this state the ventricular rate rarely exceeds 100 beats per minute after the vagi are blocked by atropine or after severe physical effort. The authors state that the rate of the ventricles during rest does not disclose whether the digitalis has caused the slowing by the "vagal" or by the "extravagal" mechanism. There are two methods for determining "extravagal" digitalization: (*a*) the atropine test, (*b*) physical exercise; after neither of these tests will the ventricular rate rise appreciably above 100 beats per minute if enough digitalis has been given to cause slowing by the "extravagal" mechanism.

Heparin and Thrombosis.

C. CRAFOORD AND E. JORPES (*The Journal of the American Medical Association*, June 28, 1941) discuss heparin as a prophylactic against thrombosis. Heparinization was carried out after surgical operation in a series of 325 cases, all the operations being on the gastro-intestinal tract or the biliary and urinary system; major operations for hernia or varices were included. The heparin used had a strength of about 70% of pure mucoitin trisulphuric acid. It was given as a 5% sterile solution four times per day. The dose, 50 *plus* 50 *plus* 50 *plus* 100 milligrammes daily, was started four hours after the operation and continued for five to ten days, care being taken to decrease the dose slowly at the end. No thromboembolic complications occurred in this series. In a control series of 1,111 similar cases such complications occurred in 9%. The authors state that 88 patients with gynæcological disorders were given heparin by P. Wetterdal. No thromboembolic complications occurred in this series, whereas in the control series of 1,054 cases the incidence of complications was 4%.

Giardiasis and "Atebrin".

H. R. HARTMAN AND F. A. KYSER (*The Journal of the American Medical Association*, June 28, 1941) present an analysis of the symptoms in 100 cases of giardiasis and the effect of treatment with "Atabrine" (English, "Atebrin"). The series consists of 100 cases encountered at the Mayo Clinic, in which *Giardia lamblia* was found in the duodenal contents, fæces or both. Fifteen patients had lesions other than giardiasis; 60% of all patients had diarrhœa, 65% had abdominal pain,

whilst other symptoms were asthenia, irritability, fever and vomiting. The authors state that they do not think that every symptom was due to giardiasis alone, but that some were entirely due to neuroses. The treatment consisted of the administration of 0·1 gramme of "Atebrin" three times per day for five days. In all but one case treatment was successful in eliminating the parasite and in giving relief from symptoms.

NEUROLOGY AND PSYCHIATRY.

The Spinal Complications of Paget's Disease.

J. W. ALDREN TURNER (*Brain*, Volume LXIII, Part 4, 1940) analyses thirteen cases of spinal compression, seven of his own and six previously reported by others, due to Paget's disease. Clinical examination revealed evidence of vertebral disease, such as rigidity and limitation of movement; in two cases there was tenderness over the upper dorsal vertebræ. The history showed gradual but relentless impairment of the functions of the cord. Numbness and weakness of the legs advanced to spasticity and the development of sphincter trouble. Pain is a common accompaniment of *osteitis deformans* of the lumbar part of the spine. Sometimes the pain is a girdle sensation. Root pains are frequent. The condition must be diagnosed from innocent spinal neoplasms and arachnoiditis. Progressive bilateral deafness is a common accompaniment of Paget's disease. The radiological appearance of the spine is characteristic. The operation of decompressive laminectomy is of value in some cases.

The Post-Concussion Syndrome.

J. M. WITTENBROOK (*The Journal of Nervous and Mental Disease*, August, 1941) believes that the post-concussion syndrome is a clinical entity; he insists that the primary pathology consists of dural adhesions. He visualizes the tearing of small blood vessels as they pass through the arachnoid with the setting up of an adhesive leptomeningitis. Six cases are presented, from which the author deduces three main symptoms — headache, dizziness and nervousness. He claims that personality changes, antisocial behaviour and narcolepsy belong to this syndrome. And he states that the majority of patients can be cured by the preparation of one or more pneumoencephalograms. In the more stubborn cases he advises the removal of adhesions by open operation.

Vitamins E and B_1 in the Treatment of Muscular Dystrophy and Motor Neurone Disease.

IN recent years a number of investigators claim to have been impressed by the value of vitamin therapy in certain diseases of the nervous system. Gerald Fitzgerald and Brian McArdle (*Brain*, Volume LXIV, Part I, 1941) sought to test the value of certain vitamins in the treatment of muscular dystrophy and motor neurone disease. Nineteen cases were studied, but no distinction was made between amyotrophic lateral sclerosis and progressive muscular atrophy, which were regarded as stages in the same disease. The results of treatment were disappointing and completely at variance with those obtained by a number of workers who had claimed clinical improvement. Patients were treated with vitamin *E* or B_1, separately or in combination, and larger doses were given than those stipulated by other workers. The daily output of creatine and creatinine was estimated, but showed no improvement.

Electrical Convulsion Therapy.

A. M. WYLLIE (*The Lancet*, July 19, 1941) compares the convulsion produced electrically with that of "Cardiazol" and "Triazol". He finds the tonic and clonic stages much the same as those produced by the chemical convulsants, though the tonic stage may be of shorter duration. At the end of the clonic stage the respiration is spontaneously reestablished. Post-convulsive restlessness and confusion follow for from five to ten minutes. The amnesia is deeper with the electrical convulsion; and although fear is not abolished, it is certainly diminished in comparison with that associated with "Cardiazol". Even if the major fit is not accomplished, amnesia is complete; and here the effect is radically different from that produced by "Cardiazol" or "Triazol", an insufficient dose of which causes very unpleasant sensations and marked apprehension and resistance to further treatment. The author claims that the spasm of an electrical convulsion is less severe than that produced by chemical means; further, such unpleasant sequelæ as fractures and dislocations and muscular pains are less common. It is claimed that there is no risk of the production of *status epilepticus*. It is suggested that short courses of electrical convulsion therapy may be the means of stabilizing those who tend to relapse after treatment. The retrograde amnesia which often follows convulsion therapy is of little significance. Most patients completely recover from this symptom within a few weeks. The results of electrical treatment applied to psychotic patients are similar to those which have been obtained for some years past by the use of chemical convulsants.

The Occurrence and Significance of Small Vascular Lesions in the Brain.

F. A. PICKWORTH (*The Journal of Mental Science*, January, 1941) marshals a number of facts of his own and of other research workers which tend to show the widespread occurrence of small vascular lesions in the brains of mental patients. He believes that similar but less extensive lesions occur in the brains of normal people suffering from a variety of septic conditions and that these lesions cause symptoms in the mental sphere which may pass unnoticed by the general run of people yet be elicited by the tactful physician. Small vascular lesions in the brain have a definite significance. They produce limitation and restriction of mental function; in some cases they lead to inappropriate behaviour to sensory stimuli, impulsive action and in many cases recognizably gross mental syndromes.

Tests of Psychomotor Efficiency in Patients Treated with "Metrazol".

J. J. O'CONNELL AND L. S. PENROSE (*The Journal of Mental Science*, April, 1941) have measured the psychomotor efficiency of patients treated with "Metrazol" ("Cardiazol") and found it to be increased. Three psycho-physiological tests were employed: determination of the reaction time to auditory stimulus, of the tapping rate and of the strength of grip. These tests touch only one aspect of the personality. Dramatic changes were noted in stuporose patients, and encouraging results were seen in cases of agitated depression. Such improvement in psychomotor efficiency was not due to the presence of the drug in the body, but persisted long after this had been excreted. The greatest improvement was noticed after the first few injections of "Metrazol"; thereafter the response tended to decline. Patients who showed the greatest improvement in psychomotor efficiency were those whose general response to the treatment was noteworthy.

Intelligence Testing in a Colony for Mental Defectives.

THE Caltell system of intelligence testing is diametrically opposed in principle to the Binet plan, and J. C. Rohan (*The Journal of Mental Science*, April, 1941) compares them from the point of view of clinical practice. His results are based on the Caltell examination of 112 patients. He considers that the test is easy to administer and that it can be simply and objectively scored. He claims that this scale marks the minimum intelligence of the subject and considers it unlikely that the intelligence rank would be lower than if measured by any other test of mental capacity. The test has the support of sound psychological principles. In a comparison of the dual testing of 98 patients by the Caltell and Binet methods a marked unevenness in the individual differences between the scores was observed and the disparity between the scores tended to become more marked as the Binet score became higher. But, making due allowances, the author considers the Caltell method satisfactory for mental testing among mental defectives.

Unilateral Exophthalmos (Proptosis).

G. JOLY DIXON (*Brain*, Volume LXIV, Part I, 1941) presents seventeen cases of proptosis of the eye. In some of these the protrusion was symmetrically forwards, in others the eye was deviated either up or down or laterally. Symmetrical proptosis may be due to (*a*) an abnormal structure inside the cone of muscles, a glioma or meningioma of the optic nerve; (*b*) lymphatic and venous engorgement of the orbit, resulting from local inflammation or obstruction to venous drainage by a lesion in the middle cranial fossa; (*c*) paresis of the ocular muscles. If the proptosed eye can be reduced into the orbit, it is probable that the cause is venous obstruction or muscular paresis, although obstruction of sufficient severity may lead to irreducible proptosis. A sudden development of proptosis argues in favour of venous or lymphatic obstruction. Papilloedema of the proptosed eye invariably occurred in tumours of the optic nerve. Visual disturbances were noted in some cases. Impairment of visual acuity was noted in conjunction with papilloedema. Central scotoma, homonymous hemianopia and bitemporal hemianopia occurred when the lesion was located in the middle cranial fossa. Diplopia and paresis were frequently associated with proptosis and pupil irregularities were found only when the lesion lay in the middle cranial fossa. Pain in the eye itself or in the forehead was constant in those cases which were due to venous occlusion.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on October 15, 1941, at the Medical Society Hall, East Melbourne, DR. H. BOYD GRAHAM, D.S.O., M.C., the Acting President, in the chair.

Liver Function and Behaviour.

PROFESSOR R. D. WRIGHT read a paper entitled "Recent Developments of Knowledge of Liver Function and Behaviour" (see page 635).

DR. IVAN MAXWELL said that Professor Wright's lecture was one of the most carefully reasoned addresses ever presented to the Victorian Branch of the British Medical Association. Dr. Maxwell then said that some years earlier he had had the privilege of meeting Dr. Mann, of the Research Department of the Mayo Clinic, and of observing animals in his laboratory which had been subjected to partial or complete hepatectomy. Dogs which were moribund after hepatectomy showed a remarkable return to an apparently normal state as the result of the intravenous injection of glucose. The human body had very little capacity to store carbohydrate; in fact, the storage was less than the amount (approximately 500 grammes) consumed in the course of twenty-four hours on an average diet; fasting for twenty-four hours would in most instances cause the appearance of ketone bodies in the urine indicative of a disorder of fat metabolism. Dr. Maxwell then referred to the fact that the liver had a vast array of enzymes within its substance, and that the union of benzoic acid with glycine to form hippuric acid, the clinical application of which Professor Wright had discussed, was due to the activity of an enzyme in the liver.

With reference to the sluice mechanism of the liver, Dr. Maxwell said that the name had been applied by Sir Henry Dale to the regulating sphincters on the hepatic veins, by means of which the outflow of blood from the liver to the inferior *vena cava* was determined. The sluice was closed by the action of histamine and opened by adrenaline, which had the power of forcing into the circulation much blood which had been stored in the liver. Dr. Maxwell went on to say that another function of the liver was the storage of the hæmatinic principle, which was of such importance in the treatment of pernicious anæmia. Furthermore, heparin was found in the liver as well as in other organs, such as the lungs, and had been used by surgeons in Canada and elsewhere to prevent post-operative embolism. In conclusion Dr. Maxwell referred to the suggestion of Best, of Toronto, that choline when administered in abundance would help to remove from the liver the excess of fat which was a feature of conditions such as phosphorus and chloroform poisoning.

DR. W. OSTERMEYER expressed his appreciation of Professor Wright's paper, which had opened a vista of the clinical applicability of physiological research work on the liver. Professor Wright had given those present an idea of the rationale of chemotherapy and many other ideas that could be incorporated in clinical medicine.

DR. H. BOYD GRAHAM, from the chair, expressed his warm appreciation of the paper and of the policy that Professor Wright had adopted, in presenting from time to time to the members of the Branch his excellent summaries of academic facts of clinical value.

Professor Wright, in reply, said that as there had been so little discussion he was at a loss to know whether he had told those present too much and tired them, or whether they had known already what he had told them. He was glad that Dr. Maxwell had mentioned the matter of the appearance of ketone bodies in the urine produced by fasting and due to defects in carbohydrate metabolism. In the fasting animal the liver poured out ketone bodies that were oxidized by the other tissues, and what appeared in the urine was relatively only a slight overflow.

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held on August 13, 1941, at the Children's Hospital, Melbourne, DR. H. DOUGLAS STEPHENS in the chair. Part of this meeting was reported in the issue of October 11, 1941.

The Tuberculin Patch Test.

DR. J. H. COLEBATCH read a paper entitled "The Tuberculin Patch Test" (see page 640).

DR. F. T. WHEATLAND said that he had been very interested in following Dr. Colebatch's work on the tuberculin patch test. Dr. Colebatch had been kind enough to go to the Commonwealth Serum Laboratories at intervals to show Dr. Wheatland the results of his tests. The patches were prepared by saturating strips of filter paper with potent and standardized tuberculin made from the filtrates of cultures of *Mycobacterium tuberculosis* grown on the synthetic medium of Dorset and Henley. The strips were dried over a solid desiccant in a dust-free system, and the process of saturation and drying was repeated. Disks having an area of one square centimetre were cut from the strips and pressed onto watreproof adhesive plaster at intervals of one per square inch. To protect the plaster and disk each patch was overlaid with canvas gauze, which could easily be removed before application of the patch. Control patches had not been provided, as they were considered unnecessary. When they had been provided, they consisted of filter paper saturated with glycerin veal broth. As no glycerin veal broth was used in the preparation of the tuberculin for the patches, it was difficult to see what they controlled.

Dr. Colebatch had mentioned the question of the stability of the tuberculin in the patches. It was well known that undiluted old tuberculin was one of the most stable of all biological products, and tests indicated that synthetic medium tuberculin was also very stable. It was thought that the tuberculin in the patches would retain its potency for a long time and that the patches might be used for a period of at least twelve months from the date of preparation. Dr. Wheatland did not think that diluted old tuberculin was as unstable as was generally believed. He thought that if it was kept sterile, and under suitable conditions, even a dilution of 1 in 1,000 would retain its potency for a considerable time. Tests carried out at the Commonwealth Serum Laboratories supported this view. Dr. Wunderly, of Adelaide, had mentioned in a paper in THE MEDICAL JOURNAL OF AUSTRALIA that he had used for the Mantoux test a dilution of 1 in 1,000 old tuberculin which he had kept for seven months, and that it had given satisfactory results. It was known that contamination of diluted tuberculin destroyed its potency, and Dr. Wheatland thought that apparent loss of potency was frequently due to minor degrees of contamination. In conclusion, Dr. Wheatland said that he was glad to have had the opportunity of hearing Dr. Colebatch's interesting paper.

DR. H. J. SINN congratulated Dr. Colebatch on the introduction of the test at the Children's Hospital. He said that they were all fortunate to have a man of his ability available to try the test. Dr. Colebatch had conducted an extensive study of the test and had even shown the lines on which further investigation should be carried out. Dr. Sinn was convinced that the new test should be incorporated in their everyday work; it would save him a considerable amount of barley sugar, which he was in the habit of using in attempting to stem the flood of tears whenever he performed Mantoux tests on little children.

DR. R. WEBSTER asked Dr. Colebatch for information about the deterioration of the tuberculin incorporated in the patch.

DR. HALLOWS expressed thanks on behalf of the surgeons; they now had another weapon to use in the establishment of the diagnosis. With clinical observation and history-taking, together with radiological and pathological investigations and the new patch test, surely the tubercle germs would not often elude detection.

Dr. Southby asked Dr. Colebatch what one should do when, after testing the children in a tuberculous household, perhaps two were found to give a positive reaction and two did not, though all had been equally in contact with the patient.

DR. BOYD GRAHAM commented on the faithfulness with which Dr. Colebatch had conducted his investigation into the value of the test. Some of that work had been done in the clinic and alongside Dr. Graham; it was a great pleasure to him to testify to its reliability and to congratulate Dr. Colebatch on the outcome.

Dr. Colebatch, in reply, thanked the members for the warm manner in which his paper had been received; its reception was distinctly encouraging to him. In reply to Dr. Webster, who had asked about the stability of old tuberculin, Dr. Colebatch said that with a fresh solution of 1 part in 1,000 dilution he had obtained positive reactions in three cases in which there had been a failure to react when a similar dilution which was not freshly prepared had been used in the wards. Unfortunately the old tuberculin was usually sold in bottles containing five cubic centimetres, which was so large an amount that it frequently had to be

kept too long. He had found the most satisfactory usual site for the test to be the front of the chest; but for younger children he had placed it over the interscapular region so that the child could not get at it if it became irritable; if the chest and back were sunburnt, he had found it desirable to apply the patches to the skin under the bathing trunks or on the inside of the upper part of the arm on skin which was not sunburnt. In reply to Dr. Southby, Dr. Colebatch remarked that those who did not react to tuberculin might be in the incubation period. That period usually lasted from three to six weeks; but if the soil was not of average fertility the incubation period might be extended considerably, even for as long as four or six months. It therefore seemed desirable that the children who failed to react on the first occasion should have the test repeated after two or three months, and radiographic investigation should be undertaken within six months of contact; radiological evidence might be obtained before the Mantoux test or the patch test produced a positive reaction. In conclusion, Dr. Colebatch said they would be apt to miss subjects unless tests for tuberculosis were carried out in routine fashion for all the children; routine testing was easier with the patch test, and he hoped that it would become the rule at the hospital.

DR. H. DOUGLAS STEPHENS, from the chair, thanked Dr. Colebatch for a contribution of outstanding merit, congratulated him on his appointment to the Australian Imperial Force, and wished him a successful career and a speedy return to his work at the hospital.

Obituary.

WILLIAM JAMES PENFOLD.

WE are indebted to Dr. R. A. Willis for the following appreciation of the late Dr. William James Penfold, whose death was recently announced in this journal.

The recent death of Dr. W. J. Penfold terminated the career of one of Australia's greatest medical scientists.

Born on September 27, 1875, at Brampton in Cumberland, Penfold passed his final examinations in medicine with honours at Edinburgh before his twentieth birthday. As he could not graduate until he was twenty-one years of age, he proceeded to the Continent for a year's study. He visited Berlin and Vienna, and in the latter city he studied pathology and bacteriology under Albrecht and Ghon respectively. He became rapidly proficient in German, in which language he always remained fluent, even to the extent of addressing medical meetings and taking part in discussions.

Returning to Edinburgh to graduate in 1896, he began practice by spending three years as a medical officer in mental hospitals, where he made over 200 post-mortem examinations of the brain. Subsequently he had a large and varied experience in clinical practice in Newcastle-on-Tyne. His first paper, on mitral and tricuspid incompetence, was published during this period. From the first Penfold felt strong leanings towards the scientific and laboratory rather than the clinical aspects of medicine; and in 1909, in spite of heavy domestic responsibilities, he went to the Lister Institute, London, first as a voluntary research worker, later as a British Medical Association scholar. In 1912 he was appointed a member of the bacteriological staff of the institute, then under the direction of Charles Martin. During his stay at the institute he also held a number of other London appointments, namely, pathologist to the Victoria Hospital for Children, where he personally conducted over 500 post-mortem examinations; pathologist to the Dental Hospital, Leicester Square; and lecturer in bacteriology in the dental school of this hospital. He was also a lecturer in the University of London and was for some time assistant editor on the staff of the *Bulletin* of the Tropical Diseases Bureau.

At the Lister Institute Penfold soon proved himself to be a scientific bacteriologist of the first rank, his papers on bacterial variation (1910-1912), on the mechanism of fever (in collaboration with Hort, 1911-1913), and on the lag phase of bacterial growth (partly in collaboration with Ledingham, 1914) gaining him world-wide recognition. In 1915 he and Ledingham, who later succeeded Martin as Director of the Lister Institute, were deputed to undertake the pathological services of the King George Military Hospital at Waterloo, the medical division of which was in the charge of Dr. C. V. Mackay, now of Melbourne. This hospital, containing nearly 2,000 beds, and receiving many Australians invalided to England with dysentery and other infections acquired in Gallipoli and Mesopotamia, gave Penfold a wide practical experience. During this period he also visited Salisbury to investigate the epidemic of cerebro-spinal fever amongst the Canadian troops, and to carry out immunization work. He was also largely responsible for designing the first mobile bacteriological laboratory used in the war.

Penfold's acceptance in 1916 of the invitation of the Commonwealth Department of Health to become the first Director of the Commonwealth Serum Laboratories at Royal Park was an event doubly fortunate for Australia, not only providing this country with a supply of vaccines, sera and other biological products of a quality equal to any in the world, but also giving us one of the best scientific brains we have had. The establishment and early development of the Serum Laboratories called for a rare combination of great scientific knowledge and good administrative ability. Penfold fortunately possessed this, and the growth of the laboratories under his direction was rapid and successful. It would be difficult to enumerate all the practical details of manufacture and technique which he developed in the work of the laboratories; but special mention must be made of his introduction of the beneficial practice of returning the blood corpuscles to horses after bleeding them for serum. The eleven years of his directorship were years of arduous practical and administrative work, giving him little scope for pure research; but even so he found time for papers on such diverse subjects as the chemical properties of the pneumococcus, the types of tubercle bacillus prevalent in Australia, an adjustable microscope tube, and the nature of cancer.

While his work at the Commonwealth Serum Laboratories was necessarily of a practical nature, Penfold did not lose the research spirit. Hence it was not surprising that, when in 1926 he was invited to become first director of the newborn Baker Research Institute at the Alfred Hospital, he accepted this post. There now began for Penfold a period of intense activity in medical research of a very varied kind, mainly in collaboration with various members of his staff and of the clinical staff of the hospital. These researches were not only in bacteriology, but also in physiological chemistry, physics, veterinary medicine and parasitology, with a direct bearing on some specific medical problem. They were tackled with the same scientific precision and thoroughness as the more abstruse and academic problems of his Lister Institute days. The subjoined list of his publications, while showing the extent and variety of his work in his new field, by no means affords a complete summary of his interests. Every branch of the laboratory and clinical work of the hospital felt the stimulus of his thought and scientific outlook. I personally, as pathologist to the hospital, soon found how profitable and stimulating it was to discuss my problems with him, for his outlook was of that broad kind which transcends the details of any one subject and makes its possessor an invaluable mentor in all fields allied to his own.

Of the many subjects which interested him during his directorship of the Baker Institute, several deserve special comment. His first task was to improve greatly the efficiency of the routine laboratory bacteriology and biochemistry of the Alfred Hospital. While Penfold himself speedily ensured this for the bacteriological section, a similar service in the biochemical section was effected by the work of Dr. A. B. Corkill, who was the senior member of his institute staff and who later succeeded him as director.

Active immunization against anaerobic bacillary infections was a problem constantly in his mind. In 1930, in a paper with Parker on black disease in sheep, he envisaged the possibility of the prevention of gas gangrene in man; and from 1935 onwards he collaborated with Miss Jean Tolhurst in a sustained research which completely demonstrated that man as well as laboratory animals could be effectively immunized against *Bacillus welchii* by two injections of an alum-precipitated formol-toxoid. He was disappointed that the military authorities did not see fit to give this method an extensive practical trial amongst the troops in the present war.

Another subject of perennial interest to him was that of blood cultures and their clinical value. Along with Miss Hildred Butler he devised a simple but efficient blood culture outfit and technique, and gave the Alfred Hospital a service in this field as near perfection as is practicable in routine hospital work. A preliminary paper on this topic in 1932 and a valuable paper on blood culture in tuberculosis in 1933 were followed in 1937 by Miss Butler's monograph, which was dedicated to Penfold in terms well illustrative of the respect and affection which he engendered in those working with him.

From 1928-1931 he was deeply interested in the now obsolete colloidal lead treatment of cancer introduced by Blair Bell. In collaboration with James Sutherland, his favourite laboratory assistant who had followed him from England to Australia and from the Commonwealth Labora-

tories to the Baker Institute, he produced a highly stable lead suspension which was used for treating a selected series of advanced cases at the Austin Hospital. He visited this hospital frequently while I was medical superintendent; this was my first personal meeting with Penfold, and I recall his thoroughness in planning his research and his anxiety that every detail of the plan should be carefully adhered to and every record made with honesty and accuracy.

In 1934, on behalf of the Melbourne and Metropolitan Board of Works, Penfold undertook an extensive research on the subject of *Tænia saginata* infestation in the population of Victoria and the possible risk of infection from the consumption of beef grown at the Werribee sewage farm. In collaboration with his son, Dr. H. B. Penfold, and with Miss Mary Phillips, this research was planned and executed with characteristic thoroughness. It not only proved the alleged risk of the consumption of beef raised on the Werribee farm to be negligible, but also led to some significant facts regarding the life history of the parasite and the development of natural immunity in animals infected by it. It must be added here that, unfortunately, as is often the case, the political action which was taken was not based on the scientific findings.

Penfold's "monograph plan" also deserves mention. This was designed to encourage workers in special fields to undertake comprehensive reviews of their subjects for publication in monograph form. The Baker Institute sponsored the scheme, a monograph fund was established, and Penfold himself undertook the task of general editorial adviser. Three monographs appeared: "Practical Anæsthesia", written by the anæsthetists of the Alfred Hospital (1932), "The Spread of Tumours in the Human Body", by the present writer (1934), and "Blood Cultures", by Miss Butler (1937). Penfold read the original drafts of these, and would not pass them for publication until they had been purged of every error of argument, syntax and punctuation which his eagle eye could discover. Had his health been maintained, it is probable that other monographs would have been added to the list; I know that he had in mind at least three further prospective writers.

Mention must also be made of his initiating a scheme for the reduction of diabetic mortality in Victoria; his interest in the development at the Baker Institute of an efficient tissue culture technique, which resulted in some excellent work by Dr. L. B. Cox and Miss Marie Cranage on the tissue culture of intracranial tumours (*The Journal of Pathology and Bacteriology*, Volume XLV, 1937); his use of the refractometer in investigating the concentrations of solutes in pathological specimens of cerebro-spinal fluid and bile; and his views on the nature of eclampsia, the convulsive characters of which he studied in a large series of experiments, and which was the subject of his last paper published in THE MEDICAL JOURNAL OF AUSTRALIA only a few weeks before his death.

Penfold's retirement in 1938 was necessitated by his failing health, dating from a severe and almost fatal attack of hemiplegia over two years earlier. In spite of this and of several subsequent attacks he retained his mental alertness and scientific interest almost to the last. He attended meetings of the Victorian Pathological Society up to a few months ago, and one of his last conscious acts was to write a letter on eclampsia which appeared in THE MEDICAL JOURNAL OF AUSTRALIA for October 25, on the day preceding his death.

Of Penfold's personal qualities the most outstanding was his uncompromising love of truth. Meticulous scientific accuracy distinguished his own work and thought, and he was outspoken in condemnation of what he deemed its lack in others. He hated diplomacy, subterfuge and compromise; and having once made a decision which he believed right on any issue, he was inflexible. This attitude was bound to offend many and to make positive enemies of some; for, being human, his own judgement sometimes erred. To those who really knew him, however, his scientific earnestness and probity could never be doubted; and to those of whose sincerity he was sure he gave generously of his store of scientific knowledge and his friendship. Penfold's love of scientific truth largely constituted his personal philosophy and rendered social success and religious orthodoxy alike needless. His fearlessness was apparent in his candour, even when he knew that his opinions would be unwelcome and likely to be to his own material disadvantage.

He was a versatile reader, especially of history and general classical literature. He loved Shakespeare; and he read many modern works also with keen enjoyment and a remarkably retentive memory. While music was denied him because of marked tone deafness, he appreciated art of the classical and realist styles, and when possible encouraged sincere young artists.

He frequently spoke to his friends of his wife's loyal support and encouragement to him in his work; and, while his fortitude during his last four years of repeated illnesses was characteristic of him, it clearly owed much to the same source.

Dr. L. B. Cox writes:

The passing of Dr. W. J. Penfold is not only a great loss to his wife and family, but to his many friends.

I first met him in 1931, when he was the Director of the Baker Institute of Research, and immediately felt his friendliness and penetrating intellect. As I knew him better I discovered his passion for that which he conceived to be the truth, and his demand for sincerity and honesty in those about him. As a leader of research he was magnificent. His enthusiasm was boundless, and he could both interest and inspire. He was as much interested in the research of others as in his own. The subject did not matter; he would read any paper submitted to him, usually for hours in the early morning, and would make the subject his own by constant study, and then deal mercilessly with syntax and unnecessary polysyllables.

He was a devastating critic of anything which seemed to him false. No paper escaped his minute analysis and unsparing criticism. Those who could withstand this *"Blitzkrieg"* might be admitted to his friendship, if they would amend their ways or justify what they had written. To those to whom he gave his friendship he was unswervingly loyal. But his strict views on scientific conduct—and indeed on human relationship in general—did not always make him friends, for his condemnation could be severe.

His passion for scientific truth usually transcended all else. On one of the last occasions on which I saw him he had suffered a coronary thrombosis a few hours before and was near to death. He began to talk to me, difficult as it was, not about his illness, but about his theory of eclampsia, and asked me to make arrangements with our friend Rupert Willis to supply him with English rabbits for this research when he was well. Even the approach of death could not dim his passion for scientific truth, and he wrote his last letter, on eclampsia, shortly before his end.

Those who knew him well will feel him to be almost irreplaceable. He was a great scientist and a great friend.

Dr. R. Fowler writes:

I first encountered Penfold at the Commonwealth Serum Laboratories, Parkville, following an introduction by Neill Fairley. I use the word "encountered" deliberately, since Penfold, courteous and inspiring as a host, did not stand on ceremony when it came to flaying me for crude pseudo-scientific utterance. This evangelist hostility towards slackness in science, together with certain other beliefs, had the effect, I fear, of repelling many acquaintances who might otherwise have become Penfold's firm friends; for those who negotiated the barrier there were constant and generous rewards.

At the time of our first meeting Penfold had just perfected a scientific contribution of immediate practical importance, namely, the restoration of washed blood corpuscles to the animal donors of therapeutic immune sera. This device was of inestimable commercial value, since it increased output whilst considerably reducing cost of production. Unhappily there was a disagreement between Penfold and the department; and ultimately he resigned from the Civil Service. Soon afterwards he was installed as first director of the Baker Institute, where he did so much. On his retirement in August, 1938, his friends induced him to sit for a portrait by A. E. Newbury, which proved to be a splendidly realistic work of art. The picture remains, but, sad to relate, both artist and subject have now passed on.

Dr. T. a'B. Travers writes:

I am pleased to be able to express my gratitude to the late Dr. W. J. Penfold.

I cannot speak of him as a bacteriologist, but to many of us his most outstanding faculty was his great critical ability. As an adviser on the construction and presentation of scientific papers he was unexcelled.

His erudition kept him familiar with the numerous branches of medicine and his enthusiasm was a delight. But above all he could see clearly the inevitable logic of scientific argument, and this, I think, was due to the essential straightness and simplicity of his own heart.

He had all the attributes of a great teacher—knowledge, enthusiasm and the art of being able to correct and instruct without hurting.

Penfold taught his own ideal—the pursuit of truth. Thus his influence remains, and his memory will always be, for me, an example and inspiration.

List of Dr. W. J. Penfold's Published Researches.

(a) *English Period.*

1903.

"Mitral and Tricuspid Incompetence", *Proceedings of the Northumberland and Durham Medical Society.*

1910.

"Studies in the Anaerobic Culture of the Intestinal Micro-organisms", *The British Medical Journal*, II.

"Variation of the Fermentation Properties of the B. Typhosus", *The British Medical Journal*, II.

1911.

"Variability in the Gas-Forming Power of Intestinal Bacteria", *Proceedings of the Royal Society of Medicine.*

"Studies in Bacterial Variation", *Journal of Hygiene*, XI.

"Dangers of Saline Injections" (with Hort), *The British Medical Journal*, II.

1912.

"On the Specificity of Bacterial Mutation", *Journal of Hygiene*, XII.

"Further Experiments on the Variability of the Gas-Forming Power of Bacteria", *Journal of Hygiene*, XI.

"Further Studies in Experimental Fever" (with Hort), *Proceedings of the Royal Society of Medicine*, London.

"A Study of the Pyrogenetic Properties of the B. Typhosus" (with Hort), *The British Medical Journal*, II.

"A Critical Study of Experimental Fever" (with Hort), *Proceedings of the Royal Society of Medicine*, V.

"The Relation of Salvarsan Fever to other Forms of Injection Fever" (with Hort), *Proceedings of the Royal Society of Medicine*, V.

"On the Chemical Action on Glucose of a Variety of B. Coli Obtained by Cultivation in Presence of a Chloracetate" (with Harden), *Proceedings of the Royal Society*, B.

1913.

"Experiment to Illustrate the Effect of Size of Population on the Rate of Selection of New Bacterial Races", *The British Medical Journal*, I.

"On the Inhibitory Action on Bacteria of Bodies Chemically Related to Monochloracetic Acid", *Journal of Hygiene*, XIII.

"The Relation of Concentration of Food-Supply to the Generation-Time of Bacteria" (with Norris), *Journal of Hygiene*, XII.

"Microorganisms and their Relation to Fever" (with Hort), *Journal of Hygiene*, XII.

1914.

"A Method of Producing Rapid and Fatal Intoxication with Bacterial Products, with Special Reference to the Cholera Vibrio" (with Violle), *The British Medical Journal*, I.

"Discussion on Variability among Bacteria and its Bearing on Diagnosis", *The British Medical Journal*, II.

"Intoxication rapide par certains produits bactériens chez les lapins en état d'hématolyse" (with Violle), *Annales de l'Institut Pasteur*, XXVIII.

"On the Nature of Bacterial Lag", *Journal of Hygiene*, XIV.

"Mathematical Analysis of the Lag Phase of Bacterial Growth" (with Ledingham), *Journal of Hygiene*, XIV.

1915.

"Two Cases of Dysentery in Children due to B. Dysenteriæ of Flexner Type", *The British Medical Journal*, II.

"Recent Bacteriological Experiences with Typhoidal Diseases and Dysentery; with Notes on the Protozoan Parasite in the Excreta" (with Ledingham and Woodcock), *The British Medical Journal*, I.

1916.

"Serological Tests in Dysentery Convalescents" (with Ledingham), *The British Medical Journal*, I.

"Further Notes on Protozoan Infections Occurring at the King George Hospital" (with Woodcock), *The British Medical Journal*, I.

"The Encystation of Entamœba Histolytica (Tetragena) as an Indication of the Vitality of the Cysts" (with Woodcock and Draw), *The British Medical Journal*, I.

"Etiology of Typhus", *Transactions of the Society of Tropical Medicine and Hygiene*, IX.

(b) *From Commonwealth Serum Laboratories, Melbourne.*

1917.

"The Establishment and Work of the Commonwealth Serum Laboratories", THE MEDICAL JOURNAL OF AUSTRALIA, II.

1921.

"Developments in the Production of Therapeutic Sera in Australia", THE MEDICAL JOURNAL OF AUSTRALIA, I.

1922.

"Hæmolytic a[illegible] Fevers" (with D. G. Robertson), THE MEDICAL JOURNAL OF AUSTRALIA, II.

"A Contribution to a Discussion on the Causation of Cancer", THE MEDICAL JOURNAL OF AUSTRALIA, I.

"The Reaction of the Pneumococcus on Aromatic Amino-Bodies", THE MEDICAL JOURNAL OF AUSTRALIA, II.

1924.

"Types of Tubercle Bacilli Prevailing in Australia", THE MEDICAL JOURNAL OF AUSTRALIA, I, Supplement.

"The Adjustable Flexion Tube Microscope", *The Australian Journal of Experimental Biology and Medical Science*, I.

(c) *From the Baker Medical Research Institute, Alfred Hospital, Melbourne.*

1928.

"Septicæmia with Recovery" (with A. B. Corkill), THE MEDICAL JOURNAL OF AUSTRALIA, I.

"Report of a Case of Typhus-Like Fever" (with A. B. Corkill), THE MEDICAL JOURNAL OF AUSTRALIA, II.

"The Baker Institute and the Laboratory Service of the Alfred Hospital", THE MEDICAL JOURNAL OF AUSTRALIA, II.

1929.

"Refractive Index of the Cerebro-Spinal Fluid" (with C. A. E. Price), THE MEDICAL JOURNAL OF AUSTRALIA, II.

"A Scheme for the Reduction of Diabetic Mortality in the State of Victoria", *Health Bulletin*, No. 19.

1930.

"A Dangerous Typhoid Carrier" (with A. Hyams), THE MEDICAL JOURNAL OF AUSTRALIA, II.

"Undulant Fever in Australia" (with Hildred M. Butler), THE MEDICAL JOURNAL OF AUSTRALIA, I.

"The Refractive Index of the Cerebro-Spinal Fluid, Used as a Check on the Chemical Analysis" (with Dorothy H. Irving), THE MEDICAL JOURNAL OF AUSTRALIA, I.

"Active Immunity against Bacillus Œdematiens, with Special Reference to Black Disease of Sheep and the Possibility of the Prevention of Gas Gangrene in Man" (with G. Parker), THE MEDICAL JOURNAL OF AUSTRALIA, II.
"The Effect of Light on Blair Bell's Colloidal Lead" (with J. Sutherland), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"The Effect of the Gamma Rays of Radium and of X Rays on Blair Bell's Colloidal Lead" (with J. Sutherland), THE MEDICAL JOURNAL OF AUSTRALIA, II.

1932.

"Blood Cultures in the Work of a General Hospital" (with Hildred M. Butler), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"The Serum Treatment of Experimental Streptococcal Infection" (with Hildred M. Butler), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"The Ætiology of Erythredema" (with Hildred M. Butler and Ian J. Wood), THE MEDICAL JOURNAL OF AUSTRALIA, II.
"A Note on Movements and Precipitations of an Amphoteric Colloid due to an Electric Field and Slight Electrolysis" (with J. Sutherland), *The Biochemical Journal*, XXVI.

1933.

"Blood Culture in Tuberculosis" (with Hildred M. Butler), THE MEDICAL JOURNAL OF AUSTRALIA, II.
"The Infection of the Placenta and of the Fœtus by Induction of Labour in Eclampsia" (with Hildred M. Butler), THE MEDICAL JOURNAL OF AUSTRALIA, I.

1935.

"Medical Research in Australia" (Bancroft Memorial Lecture), THE MEDICAL JOURNAL OF AUSTRALIA, II.
"Extract from Report on the Apparent Outbreak of Cysticercus Bovis in 1933 at the Melbourne and Metropolitan Board of Works Farm, Werribee."

1936.

"The Diagnosis of Tænia Saginata Infestation" (with H. B. Penfold), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"A Survey of the Incidence of Tænia Saginata Infestation in the Population of the State of Victoria from January, 1934, to July, 1935" (with H. B. Penfold and Mary Phillips), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"Acquired Active Immunity in the Ox to Cysticercus Bovis" (with H. B. Penfold and Mary Phillips), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"Ridding Pasture of Tænia Saginata Ova by Grazing Cattle or Sheep" (with H. B. Penfold and Mary Phillips), *The Journal of Helminthology*, XIV.

1937.

"Cysticercus Bovis and its Prevention" (with H. B. Penfold and Mary Phillips), *The Journal of Helminthology*, XV.
"Tænia Saginata: Its Growth and Propagation" (with H. B. Penfold and Mary Phillips), *The Journal of Helminthology*, XV.
"The Criteria of Life and Viability of Mature Tænia Saginata Ova" (with H. B. Penfold and Mary Phillips), THE MEDICAL JOURNAL OF AUSTRALIA, II.
"Artificial Hatching of Tænia Saginata Ova" (with H. B. Penfold and Mary Phillips), THE MEDICAL JOURNAL OF AUSTRALIA, II.
"Placental Infection in Induced Labour, with Special Reference to its Relationship to Fœtal and Neo-Natal Mortality" (with Hildred M. Butler), THE MEDICAL JOURNAL OF AUSTRALIA, II.
"Formol-Toxoids in the Prophylaxis of Gas Gangrene" (with Jean C. Tolhurst), THE MEDICAL JOURNAL OF AUSTRALIA, I.

1938.

"The Distribution of Cysticercus Bovis in the Sites of Election in the Ox" (with H. B. Penfold and Mary Phillips), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"Refractometry and Concentration of the Bile" (with J. Sutherland), THE MEDICAL JOURNAL OF AUSTRALIA, I.
"The Prophylaxis of Gas Gangrene in Man" (with Jean C. Tolhurst), THE MEDICAL JOURNAL OF AUSTRALIA, I.

1941.

"Active Immunisation against Gas Gangrene and Tetanus" (with Jean C. Tolhurst and D. Wilson), *The Journal of Pathology and Bacteriology*, LII.
"On the Nature of Eclampsia", THE MEDICAL JOURNAL OF AUSTRALIA, II.

GLADSTONE RUSSELL GILLIES.

WE regret to announce the death of Dr. Gladstone Russell Gillies, which occurred on November 25, 1941, at Concord, New South Wales.

LANGLOH PARKER JOHNSTON.

WE regret to announce the death of Dr. Langloh Parker Johnston, which occurred on November 29, 1941, at Sydney, New South Wales.

Naval, Military and Air Force.

CASUALTIES.

ACCORDING to the casualty list recently published, Surgeon Commander J. R. Hasker, R.A.N., of Victoria, and Surgeon Lieutenant-Commander F. H. Genge, R.A.N., of New South Wales, are reported missing and must be assumed lost.

Notice.

THE New South Wales Post-Graduate Committee in Medicine announces that the next library seminar arranged by the Post-Graduate Directors of Medicine, Surgery and Pathology will be held at the Prince Henry Hospital, Little Bay, New South Wales, on Monday, December 8, 1941, at 4.30 o'clock p.m. In these seminars, which are quite informal, special attention is given to recent literature, and it is the aim of the directors to encourage free discussion on the selected subjects.

A cordial invitation to be present is extended to all medical practitioners.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Kenny, Patrick John, M.B., B.S., 1936 (Univ. Sydney), NX70399, Captain, A.A.M.C., 2 Australian General Hospital, Australian Imperial Force, Abroad.

Hellestrand, Jean Marian, M.B., B.S., 1941 (Univ. Sydney), Rachel Forster Hospital, Redfern.

Books Received.

"The Story of the Red Cross", by Joan and Daryl Lindsay; 1941. Melbourne: The Australian Red Cross Society. Demy 4to, pp. 104, with many illustrations. Price: 7s. 6d.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.